NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Latanoprost-netarsudil for previously treated open-angle glaucoma or ocular hypertension [ID1363]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Latanoprost-netarsudil for previously treated open-angle glaucoma or ocular hypertension [ID1363]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from Santen:
   a. Full submission
   b. Cost Comparison submission
   c. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions from:**
   a. Glaucoma UK

4. **External Assessment Report** prepared by Aberdeen HTA Group

5. **External Assessment Report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from company**

7. **Technical engagement responses from stakeholders:**
   a. Royal College of Ophthalmologists and UK & Eire Glaucoma Society – joint response

8. **Technical engagement responses and statements from experts**:
   a. Neeru Vallabh – clinical expert, nominated by Santen
   b. Anthony Khawaja – clinical expert, nominated by Santen
   c. Joanna Hodgkinson – patient expert, nominated by Glaucoma UK (*see document 4a.*)
   d. Julia Margetts – patient expert, nominated by Glaucoma UK (*see document 4a.*)

9. **External Assessment Report critique of company response to technical engagement** prepared by Aberdeen HTA Group

10. **External Assessment Report critique of company Cost Comparison submission** prepared by Aberdeen HTA Group

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Netarsudil-latanoprost for previously treated open-angle glaucoma or ocular hypertension [ID1363]

Document B

Company evidence submission

June 2023

File name	Version	Contains confidential information	Date
ID1363_Netarsudil-latanoprost_Document B_v1.0_AIC_CIC_redacted_27JUN23	v1.0	Yes	27/06/23

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Abbreviations

AE	Adverse event
AH	Aqueous humor
ALT	Argon laser trabeculoplasty
ANCOVA	Analysis of Covariance
BB	Beta blocker
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COAG	Chronic open-angle glaucoma
DDTAE	Discontinuation due to adverse events
DSU	Decision Support Unit
EGS	European Glaucoma Society
EMA	European Medicines Agency
ERG	Evidence Review Group
ESS	Effective sample size
ETDRS	Early Treatment Diabetic Retinopathy Study
EVP	Episcleral venous pressure
FDC	Fixed-dose combination
FSH	Follicle-stimulating hormone
HCRU	Healthcare resource use
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
HTA	Health Technology Assessment
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
IOP	Intraocular pressure
IPD	Individual patient-level data
ITC	Indirect treatment comparison
ITT	Intention-to-treat
LASIK	Laser-assisted in situ keratomileusis
LOCF	Last observation carried forward
LS	Least square
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MCMC	Markov Chain Monte Carlo
NEI	National Eye Institute
NHS	National Health Service
NHSCII	NHS cost inflation index
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
OAG	Open-angle glaucoma
OHT	Ocular hypertension
OHTS	Ocular Hypertension Treatment Study
OTC	Over-the-counter
OWSA	One-way sensitivity analysis
PGA	Prostaglandin analogue
PLD	Patient-level data
POAG	Primary open-angle glaucoma
PP	Per-protocol
PPK	Photorefractive keratectomy
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QD	Once daily
QoL	Quality of life
RCT	Randomised controlled trial
RhoA	Ras homolog family member A
ROCK	Rho-(associated) coiled-coil containing protein kinase
RNFL	Retinal nerve fibre layer
SAE	Serious adverse event
SC	Schlemm’s canal
SD	Standard deviation
SE	Standard error
SF-36	Short Form-36
SLR	Systematic literature review
SLT	Selective laser trabeculoplasty
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SOC	System organ class
STC	Simulated treatment comparison
TEAE	Treatment-emergent adverse event
TM	Trabecular meshwork
UD	Unit dose
UK	United Kingdom
WTP	Willingness-to-pay

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. Further details of the decision problem are presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with primary open-angle glaucoma or ocular hypertension whose intraocular pressure (IOP) has not improved after treatment with a prostaglandin or netarsudil	Adult patients with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction	Wording used to align with the marketing authorisation
Intervention	Netarsudil-latanoprost (Roclanda®)	Netarsudil-latanoprost (Roclanda®)	In line with the NICE final scope

Comparator(s)	• Topical (eye drops), monotherapy or in combination:
	  ○ Prostaglandin analogues (for example bimatoprost, latanoprost, tafluprost, travoprost)
	  ○ Beta-blockers (for example betaxolol, carteolol hydrochloride, levobunolol hydrochloride, timolol maleate)
	  ○ Carbonic anhydrase inhibitors (for example acetazolamide, brinzolamide, dorzolamide)
	  ○ Sympathomimetics (for example apraclonidine, brimonidine tartrate).
	• Selective laser trabeculoplasty
	• Other glaucoma surgery
		• FDC topical eye drops:
		  ○ Prostaglandin analogues (for example bimatoprost, latanoprost, tafluprost, travoprost)
		  ○ Beta-blockers (for example betaxolol, carteolol hydrochloride, levobunolol hydrochloride, timolol maleate)
		  ○ Carbonic anhydrase inhibitors (for example acetazolamide, brinzolamide, dorzolamide)
		  ○ Sympathomimetics (for example apraclonidine, brimonidine tartrate).
			Netarsudil-latanoprost is licensed in adult patients for whom monotherapy with a prostaglandin or netarsudil has failed due to insufficient IOP reduction.[1] Therefore, it is not appropriate to consider topical monotherapies as comparators, since netarsudil-latanoprost will be offered once patients have failed on these. Furthermore, clinical expert opinion has advised that in UK clinical practice, netarsudil-latanoprost will be positioned in adult patients for whom free combination therapy has failed due to insufficient adherence. Netarsudil-latanoprost will therefore be positioned alongside other fixed-dose combination topical therapies, as aligned with UK clinical expert opinion.
			
			Selective laser trabeculoplasty and other glaucoma surgery are also not appropriate to consider as comparators as these will be offered to patients on top of or after treatment with netarsudil-latanoprost

			or other fixed-dose combination topical therapies.
Outcomes	The outcome measures to be considered include: • Mean IOP • Visual acuity • Visual field test • Evaluation of anterior and posterior segment parameters • Structural integrity of the optic nerve • Adverse effects of treatment • HRQoL	In line with the primary and secondary endpoints in MERCURY 3, the following outcomes are captured in the economic model and the submission: • IOP • AEs • HRQoL	In line with the NICE final scope.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	A cost-utility analysis was conducted in Microsoft Excel with the cost-effectiveness expressed in terms of an incremental cost per quality-adjusted life year. A lifetime time horizon was used (33 years). The analysis considers the benefit of treatment in the best and worst seeing eye. Costs were considered from an National Health Service and Personal Social Services perspective. Costs of biosimilar and generic products were taken into account.	In line with the NICE final scope.

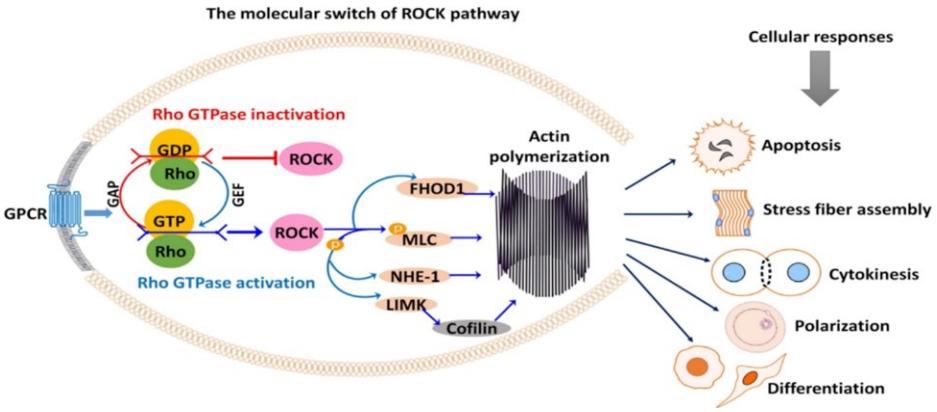
	Cost-effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.		
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • Adult patients with primary open-angle glaucoma for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction. • Adult patients with ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction.	The evidence did not allow for subgroups to be considered.	In line with the NICE final scope.
Special considerations including issues related to equity or equality	Adults with primary open-angle glaucoma or ocular hypertension whose IOP has not improved after treatment with a prostaglandin or netarsudil	Adult patients with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction	Wording used to align with the marketing authorisation

Abbreviations: AE – adverse event; HRQoL – health-related quality of life; IOP – Intraocular pressure; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; UK – United Kingdom

B.1.2 Description of the technology being appraised

Table 2 presents a brief description of netarsudil-latanoprost. The Summary of Product Characteristics (SmPC) can be found in Appendix C.

Table 2: Technology being appraised

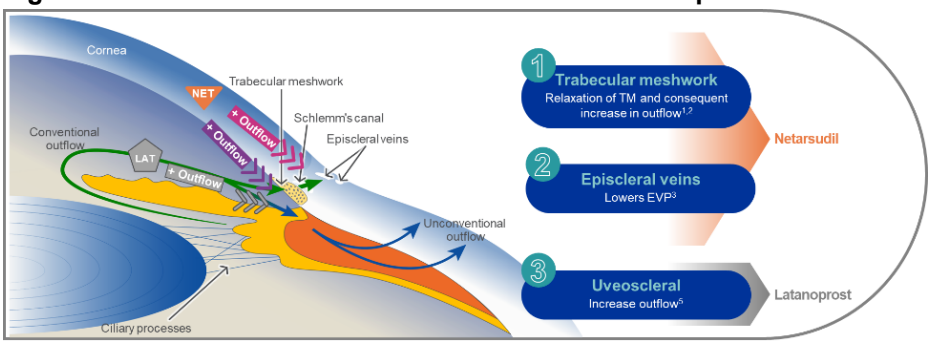
UK approved name and brand name	Netarsudil-latanoprost (Roclanda®)
Mechanism of action	Roclanda contains two active substances: netarsudil, a Rho-(associated) coiled-coil containing protein kinase (ROCK) inhibitor, and latanoprost, an isopropyl ester prodrug. These two components lower IOP by increasing the outflow of aqueous humor (AH), via different mechanisms of action. The combined effect of the two components results in additional IOP reduction compared to either compound administered alone, across the conventional (netarsudil) and unconventional (latanoprost) outflow.[1] In a healthy eye, the trabecular meshwork (TM) is responsible for approximately 70-96% of AH outflow.[2–4] In the glaucomatous eye, the TM undergoes structural changes which leads to increased resistance in AH outflow. ROCKs were originally identified as downstream effectors of the Ras homolog family member A (RhoA) small GTPase. Rho-GTPase binds to ROCK (ROCK 1/2) to stimulate over 60 downstream effectors including ROCK. ROCKs are involved in a number of diverse cellular activities including actin cytoskeleton organisation, cell adhesion and motility, proliferation and apoptosis, remodelling of the extracellular matrix and smooth muscle cell contraction. Activation of the Rho/ROCK signalling pathway can lead to increased AH outflow resistance (Figure 1).[5–11] **Figure 1: ROCK pathway**  Abbreviations: GAP – guanine-nucleotide exchange factors; GDP – guanosine diphosphate; GEF – GTP-ase activating proteins; GPCR – G-protein-coupled receptors; GTP – guanosine triphosphate; LIMK – LIM kinase; MLC – myosin light-chain; ROCK – Rho-associated protein kinase. Figure reproduced from Saadeldin *et al.* (2021)[12] ROCK inhibitors act on Rho kinase by altering the conformation of the protein, disrupting translocation to the plasma membrane, preventing ATP-dependent phosphorylation and blocking RhoA binding to ROCK, preventing downstream actions.[13]

Netarsudil is both a potent inhibitor of ROCK1 and ROCK2 and a norepinephrine transporter (NET) inhibitor that specifically targets the conventional trabecular pathway of AH outflow. Netarsudil has the following mechanisms of action[14,15]:

- Increases TM outflow through:
  - Relaxation of the TM and contraction of the ciliary muscle leads to an increase in AH outflow through the conventional pathway.
  - Changes in the actomyosin cytoskeleton and cell adhesive properties which lead to a decrease in actin stress fibres and focal adhesions in the TM outflow cells and expansion of the opening to conventional outflow tissues. The cross-sectional area of the Schlemm's canal (SC) is increased which prevents collapse.
- Lowers elevated episcleral venous pressure (EVP) by:
  - Reducing the resistance at the SC/juxtacanalicular connective tissue 1 (JCT1).
  - Increasing the flow in both the SC and scleral vessels that conduct AH outflow by disrupting focal adhesions in the inner endothelial lining.

The mechanisms of action of netarsudil and latanoprost are summarised in Figure 2.

Figure 2: Mechanism of action of netarsudil and latanoprost



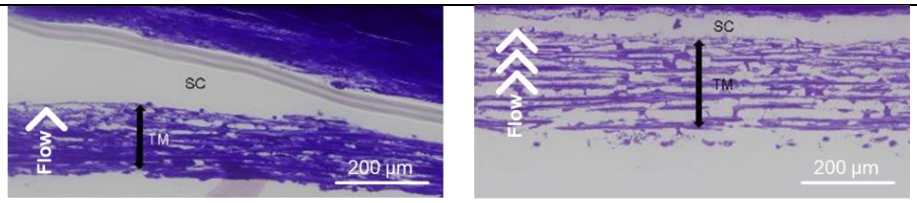
Abbreviations: EVP – episcleral venous pressure; LAT – latanoprost; NET – netarsudil; TM – trabecular meshwork.

Figure reproduced from Rao *et al.* (2017), Rao *et al.* (2007), Sit *et al.* (2019), Wang *et al.* (2015), Toris *et al.* (2008)[16–20]

An imaging study published in 2020 showed that netarsudil affects AH outflow in the tissue of the TM by inducing phagocytosis and/or modulating cell communication in the TM via actin-rich extracellular vesicles and thin membrane channels (tunnelling nanotubes) (Figure 3). These cellular functions interact in the regulation of IOP in both healthy and glaucomatous eyes.[15]

During light microscopy experiments in enucleated donor human eyes, perfusion with netarsudil-M1 (netarsudil's active metabolite) caused expansion of the TM tissue and reduced the distal resistance of the TM outflow pathway.[21] It is also important that netarsudil has been shown to lower EVP in both healthy and glaucomatous eyes, a novel effect on the distal part of the conventional outflow pathway that forms a lower limit for the reduction of IOP.[22–24]

Figure 3: Light microscopic image of netarsudil-treated eyes

	 +Control* + Netarsudil-M1 Abbreviations: SC – Schlemm's canal; TM – trabecular meshwork. Figure reproduced from Ren *et al*. (2016)[15] Latanoprost is an isopropyl ester prodrug which per se, is inactive but becomes biologically active after hydrolysis to the acid form. The prodrug is well-absorbed through the cornea, and all active substance that enters the AH is hydrolysed during passage through the cornea. Studies in animal and man indicate that the main mechanism of action for latanoprost, a prostaglandin F2-alpha analogue, is increased uveoscleral outflow, although some increase in outflow facility (decrease in outflow resistance) has been reported in humans.[1]
Marketing authorisation/CE mark status	Netarsudil-latanoprost (Roclanda) received a positive Committee for Medicinal Products for Human Use (CHMP) opinion on 12th November 2020. The regulatory approval by the European Commission was granted via the European Commission Decision Reliance Procedure on 8th January 2021.
Indications and any restriction(s) as described in the SmPC	Netarsudil-latanoprost is indicated for the reduction of elevated IOP in adult patients with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction.[1]
Method of administration and dosage	Netarsudil-latanoprost is for ocular use only. If netarsudil-latanoprost is to be used concomitantly with other topical ophthalmic medicinal products, each medicinal product should be administered at least five minutes apart. Due to netarsudil's vasodilating properties, other eye drops should be administered before netarsudil-latanoprost. Eye ointments should be administered last. Contact lenses should be removed prior to instillation of netarsudil-latanoprost and may be reinserted 15 minutes following its administration. As with any eye drops, to reduce possible systemic absorption, it is recommended that the lachrymal sac be compressed at the medial canthus (punctal occlusion) for one minute. This should be performed immediately following the instillation of each drop. The tip of the dispensing container should avoid contacting the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. The recommended dosage is one drop in the affected eye(s) once daily in the evening. Patients should not instil more than one drop in the affected eye(s) each day. If one dose is missed, treatment should continue with the next dose in the evening.[1]
Additional tests or investigations	Netarsudil-latanoprost can be prescribed to patients in line with its marketing authorisation without the need for additional tests or investigations.

List price and average cost of a course of treatment	The list price for netarsudil-latanoprost is £14.00 per 2.5 ml bottle.[25] The annual cost of treatment is £204.54 at the list price (based on a monthly total cost of £17.05).
Patient access scheme (if applicable)	Not applicable.

Abbreviations: AH – Aqueous humor; CE – Cost-effectiveness; CHMP – Committee for Medicinal Products for Human Use; EVP – Episcleral Venous Pressure; IOP – Intraocular pressure; OH – Ocular hypertension; ROCK – Rho-associated kinase; SC – Schlemm's canal; SmPC – Summary of Product Characteristics; TM – Trabecular meshwork; UK – United Kingdom

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Glaucoma and IOP

Glaucoma refers to a group of progressive and irreversible eye conditions characterised by damage to the optic nerve.[26] It can lead to visual field loss and is a major cause of visual impairment including decreased vision and blindness.[27] Glaucoma is usually associated with an increase in pressure within the eye, known specifically as IOP. This can be caused by either the production of too much aqueous humor (AH) by the ciliary body or decreased outflow (drainage) of the fluid.[28] A build-up of too much pressure in the eye is what specifically causes damage to the optic nerve.

An IOP measure of between 11 and 21 mmHg is considered normal, and diurnal variance of IOP is expected, with higher pressures typically found in the morning.[28] Elevated IOP (i.e., IOP > 21 mmHg) is considered the most significant risk factor for developing glaucoma.[29] Therefore controlling IOP is critical to prevent progression to glaucoma and damage to the eye.

The three main pharmaceutical mechanisms to control IOP are as follows: (1) increasing AH outflow via the TM pathway, (2) increasing AH outflow via the uveoscleral outflow pathway, or (3) decreasing the production of AH. IOP is regulated by balancing AH production in the ciliary body and AH outflow primarily through the TM, and to a lesser extent through the uveoscleral pathway.[30] The TM is responsible for approximately 70-96% of AH outflow and therefore, dysfunction of the TM in a glaucomatous eye is a major cause for an increase in IOP.[2–4] In glaucoma patients, AH outflow through the TM is reduced, resulting in elevated IOP.[30] The pressure lowering medications currently available are unable to successfully lower IOP especially in the long-term, regardless of treatment combinations, mechanisms of action, and analogues. At present, netarsudil, a ROCK inhibitor, is the only molecule licensed in glaucoma that reduces IOP by increasing outflow through the TM. It does this by expanding the juxtacanalicular tissue of the TM and dilating the episcleral veins.[15,24] Other drugs such as pilocarpine increase trabecular outflow by acting on the ciliary muscle and not directly on the juxtacanalicular tissue. The combination of a ROCK inhibitor with a prostaglandin analogue could potentially maximise the benefit of increased outflow. Currently available fixed-dose combination (FDC) topical treatments for glaucoma do not contain netarsudil and hence, do not act directly on the TM to reduce IOP, highlighting an urgent and important unmet need. Netarsudil-latanoprost is the first FDC whose mechanism of action targets dysfunction of the

TM and as such, should be considered as an early FDC treatment option in patients with primary open-angle glaucoma (POAG) and ocular hypertension (OHT). A more significant reduction in IOP is associated with a better long-term prognosis. Besides that, the rate of retinal nerve fibre layer loss, which naturally thins with age, is faster in the presence of increased IOP especially in glaucoma patients.[31] A 1 mmHg increase in IOP has been estimated to be associated with a 0.051 µm per year faster loss of retinal nerve fibre layer loss.[31] There is therefore a clear benefit to maintaining a sustained lower IOP and starting at an early treatment stage.

Primary open-angle glaucoma

POAG is defined by the European Glaucoma Society (EGS) as a chronic, progressive, potentially blinding, irreversible eye disease causing optic nerve rim and retinal nerve fibre layer (RNFL) loss, with related visual field defects. As well as elevated levels of IOP, other major risk factors include older age, ethnicity, and family history. For POAG, the pathology underlying increased IOP resides in the TM.[32] Visual disability is usually prevented by early diagnosis and treatment.[33]

In the United Kingdom (UK), POAG is the most common form of glaucoma. It is estimated that about 2% of people aged 40 years or over have POAG, and this rises to almost 10% in people older than 75 years.[34] Around half of all people in the UK with POAG have not been diagnosed, as people with the condition are typically unaware that they have it.[35,36] Detection of POAG is opportunistic, and is most frequently identified by optometrist assessment in the community.[37] It is important to treat POAG as early as possible to prevent permanent damage to the eyes.

Ocular hypertension

OHT is the term used to describe elevated IOP, that is, IOP greater than 21 mmHg in the absence of optic nerve damage or visual field loss.[38] OHT can be present for many years without the development of glaucoma, however sustained elevation of IOP causes damage to the optic nerve head and is a major risk factor for the development of POAG.[28] Other risk factors for OHT developing into POAG includes corneal thickness and age.[29]

In the UK, OHT affects about 3-5% of people aged 40 years or over.[39] Treating patients with OHT is key in order to reduce the risk of progression into POAG, as demonstrated by the Ocular Hypertension Treatment Study (OHTS). Results from this study showed that the 5-year cumulative probability of developing POAG in untreated OHT patients was 9.5% compared to 4.4% in treated OHT patients, demonstrating that if OHT is treated appropriately, then the risk of progression to POAG is reduced by approximately half.[40]

Patients with POAG or OHT who have elevated IOP despite existing treatment, are at continued high risk of vision loss.

B.1.3.2 Humanistic burden of disease

Health-related quality-of-life burden due to POAG and OHT

Patients with POAG or OHT face significant challenges on a daily basis due to their conditions. As vision starts to deteriorate, this has a detrimental effect on a patient's ability to walk,

balance, read, drive, and limits their ability to carry out tasks such as grocery shopping and their employment. When walking becomes difficult, there is a higher risk of falls which restricts patients from engaging in physical activity, subsequently leading to a reduction in quality-of-life, an increase in morbidity and ultimately, could lead to an increased risk of mortality.[41]

These conditions also have a negative impact on the psychological, social, and emotional functioning of patient's, resulting in anxiety, poor self-image, poor psychological well-being, and reduced confidence in healthcare.[42] A diagnosis of POAG or OHT itself increases anxiety, and up to 80% of patients describe negative emotions upon receiving this, as they worry about possible blindness as a result.[43]

Studies have shown that the quality-of-life in POAG or OHT patients is often affected by the impairment of visual function, and as the severity of the conditions increases.[44] This highlights the importance of treatments that can lower IOP effectively to slow disease progression, which in turn should help to improve the quality-of-life of POAG or OHT patients.

B.1.3.3 Economic burden of disease

Economic burden due to POAG and OHT

There are considerable costs to the healthcare system associated with POAG and OHT. Glaucoma care currently accounts for an estimated 20% of hospital eye service outpatient visits in the UK, with over 1 million glaucoma-related outpatient visits made each year to hospital eye services in England.[45] In 2016, the average annual cost incurred by five National Health Service (NHS) hospital trusts per POAG patient was £444, with the majority of this cost attributed to medical staff services. For OHT patients, this cost was £320, with medical staff services again making up the bulk of the cost.[46] These estimates are expected to rise over the coming years due to an ageing population, increased access to sight testing, and more rigorous optometry screening.[47] Furthermore, the COVID-19 pandemic resulted in thousands of glaucoma outpatient attendances being deferred, meaning that there is currently a significant backlog of patients awaiting follow-up appointments.[46]

Modelling projections estimate that the number of people with glaucoma in the UK is expected to rise by 44% between 2015 and 2035, which will ultimately have a significant economic impact on the NHS.[48] Therefore there is a high unmet need for an effective treatment for patients with POAG or OHT to reduce this burden on the healthcare system.

B.1.3.4 Clinical pathway of care

The only modifiable risk factor for POAG or OHT is to reduce IOP within the anterior chamber of the eye, with the overall aim of treatment being to preserve sight. Achieving a reduction in IOP reduces pressure on the optic nerve and helps to stop further damage.

As previously described, the three main pharmaceutical mechanisms to control IOP are as follows: (1) increasing AH outflow via the TM pathway, (2) increasing AH outflow via the uveoscleral outflow pathway, or (3) decreasing the production of AH. In particular, the TM is responsible for approximately 70-96% of AH outflow.[2–4] Currently available FDC topical treatments do not act on the TM, highlighting an urgent unmet need for a new treatment which does so.

Management of POAG and OHT requires individualised, chronic, life-long treatment with a spectrum of therapeutic options including medications (such as prostaglandin analogues [PGAs], beta-blockers [BBs], carbonic anhydrase inhibitors [CAIs], sympathomimetics), laser treatment (selective laser trabeculoplasty [SLT]) and surgery (trabecular stent bypass microsurgery).[39] The common goal amongst the various therapies is to lower IOP in order to prevent visual field loss in patients with OHT, and progression of field loss in patients with POAG. The impact of glaucoma on daily life is major, and minimisation of adverse effects associated with treatment is essential.

POAG treatment guidelines

The current National Institute for Health and Care Excellence (NICE) treatment pathway for patients with POAG is presented in Figure 4, with a summary provided below.[39]

For patients with newly diagnosed POAG:

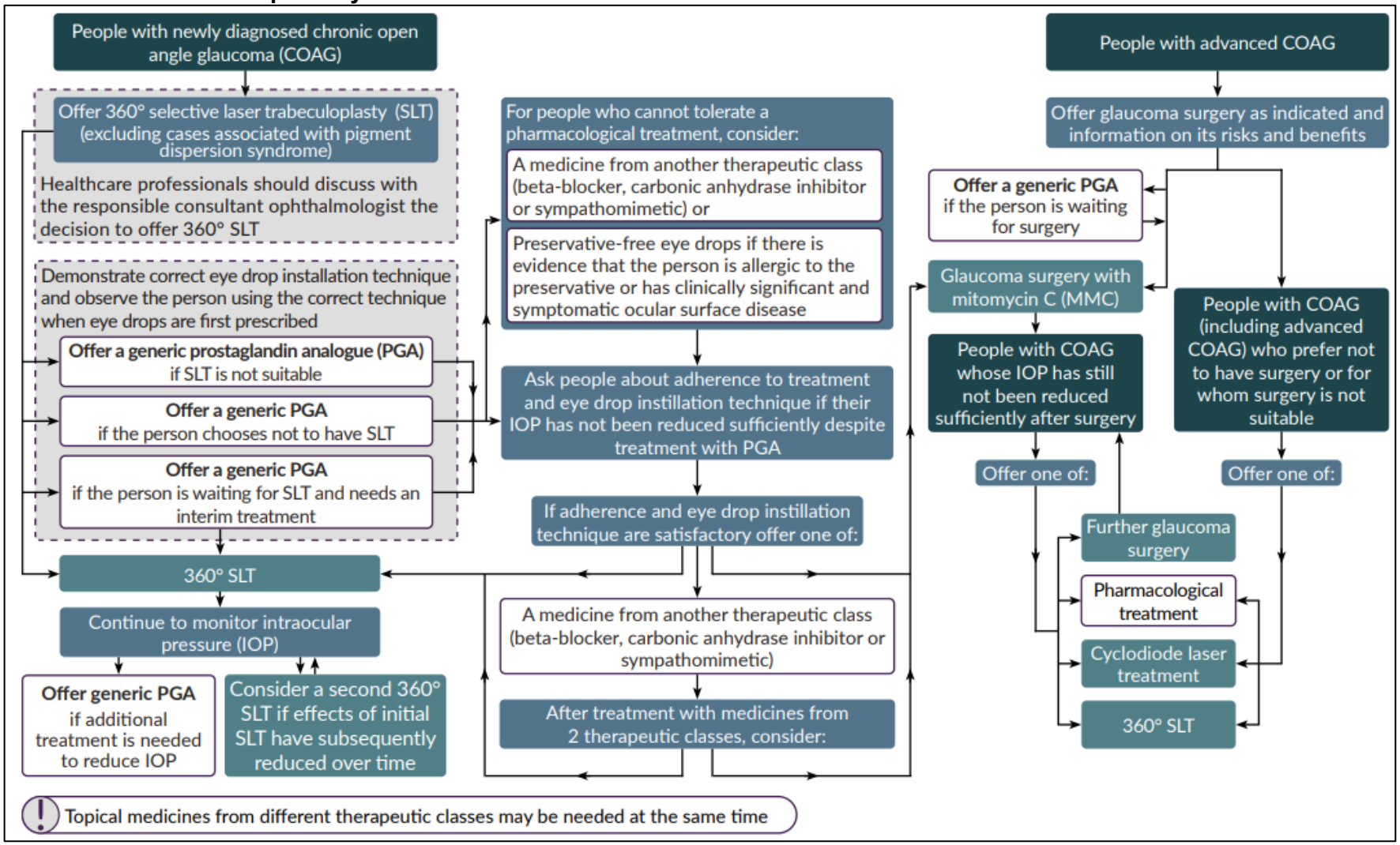
- Patients will be offered SLT if it is deemed suitable by the consultant ophthalmologist (excluding cases associated with pigment dispersion syndrome)
    - Following this, IOP will continue to be monitored. A generic topical treatment (typically a PGA) will be offered if needed to reduce IOP (either as monotherapy or as a combination with another treatment class), or a second SLT procedure will be considered if the effects of initial SLT have subsequently reduced over time
- A generic topical monotherapy (typically a PGA) will be offered to patients for whom SLT is not suitable, for those choosing not to have SLT, and for those who require an interim treatment whilst waiting for SLT
    - For patients who cannot tolerate their current treatment, a monotherapy treatment from a different class can be considered such as a BB, CAI, or sympathomimetic. Alternatively, preservative-free eye drops can be used if there is evidence that the person is allergic to the preservative or has clinically significant and symptomatic ocular surface disease
    - For patients taking topical monotherapy, they will be asked about adherence to treatment and eye drop instillation technique if their IOP has not been reduced sufficiently. If they are adherent, they will be offered one of the following:
        - A medicine from another therapeutic class either as monotherapy or a combination
        - SLT
        - Glaucoma surgery with mitomycin C
    - Treatment with SLT or glaucoma surgery will also be offered to patients after treatment with medicines from two therapeutic classes have been tried

For patients with advanced POAG:

- Offer glaucoma surgery with mitomycin C

    - A generic topical treatment (typically a PGA) will be offered if needed to reduce IOP (either as monotherapy or as a combination with another treatment class) for patients who are waiting for surgery
    - Offer one of the following to people with POAG whose IOP has not been reduced sufficiently to prevent the risk of progression to sight loss after glaucoma surgery:
        - Pharmacological treatment, either as monotherapy or as a combination with another treatment class
        - Further glaucoma surgery
        - SLT
        - Cyclodiode laser treatment
- Offer one of the following to patients who prefer not to have glaucoma surgery or for whom glaucoma surgery is not suitable:
        - Pharmacological treatment, either as monotherapy or as a combination with another treatment class
        - SLT
        - Cyclodiode laser treatment

Figure 4: Current treatment pathway for POAG[39]



Note: COAG is another term used for POAG.

Abbreviations: COAG – Chronic open-angle glaucoma; IOP – Intraocular pressure; MMC – Mitomycin C; PGA – Prostaglandin analogue; POAG – Primary open-angle glaucoma; SLT – Selective laser trabeculoplasty

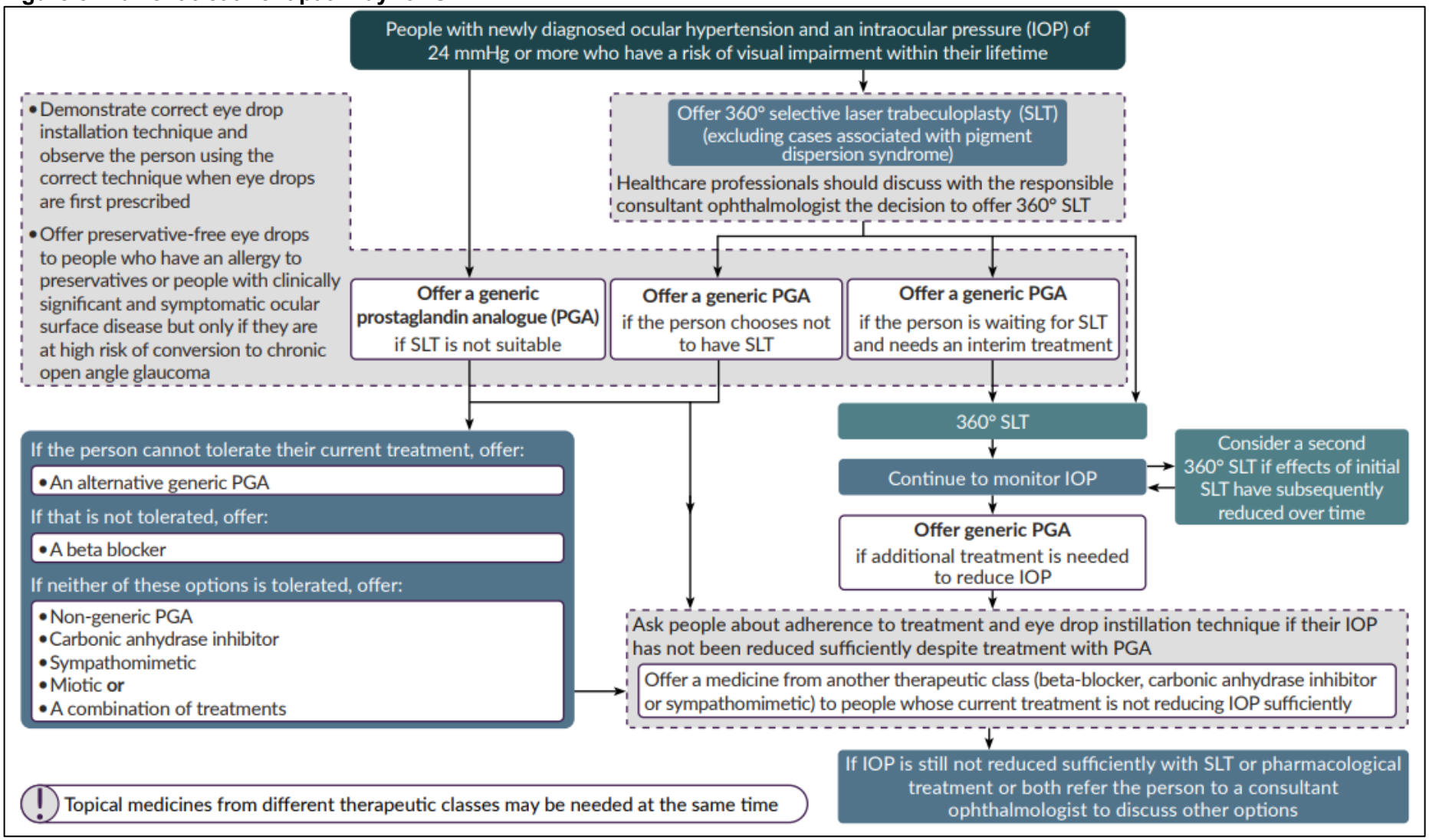
OHT treatment guidelines

The current NICE treatment pathway for patients with OHT is presented in Figure 5, with a summary provided below.[39]

For patients with newly diagnosed OHT and an IOP of 24 mmHg or more who have a risk of visual impairment within their lifetime:

- Patients will be offered SLT if it is deemed suitable by the consultant ophthalmologist (excluding cases associated with pigment dispersion syndrome)
    - Following this, IOP will continue to be monitored. Consider a second SLT procedure if the effect of an initial successful SLT has subsequently reduced over time
    - If additional treatment is needed to reduce IOP sufficiently to prevent the risk of visual impairment, then offer a generic PGA
    - For patients taking a generic PGA, they will be asked about adherence to treatment and eye drop instillation technique if their IOP has not been reduced sufficiently. If they are adherent, they will be offered a medicine from another therapeutic class (BB, CAI, or sympathomimetic) either as monotherapy or as a combination
- Offer a generic PGA monotherapy to patients for whom SLT is not suitable, for those choosing not to have SLT, and for those who require an interim treatment whilst waiting for SLT. Offer preservative-free eye drops to people who have an allergy to preservatives or people with clinically significant and symptomatic ocular surface disease but only if they are at high risk of conversion to POAG
    - For patients who cannot tolerate PGA monotherapy, offer an alternative generic PGA. If this is not tolerated, offer BB monotherapy. If this is also not tolerated, then offer one of the following:
        - A non-generic PGA
        - A CAI
        - A sympathomimetic
        - A miotic
        - A combination of treatments
    - For patients taking topical monotherapy or combinations, they will be asked about adherence to treatment and eye drop instillation technique if their IOP has not been reduced sufficiently. If they are adherent, they will be offered a medicine from another therapeutic class (BB, CAI, or sympathomimetic) either as monotherapy or as a combination
- If IOP is still not reduced sufficiently with SLT or pharmacological treatment or both, refer the person to a consultant ophthalmologist to discuss other options to prevent the risk of progression to sight loss

Figure 5: Current treatment pathway for OHT[39]



Abbreviations: IOP – Intraocular pressure; OHT – Ocular hypertension; PGA – Prostaglandin analogue; SLT – Selective laser trabeculoplasty

Despite the large number of topical treatments available to treat POAG and OHT, there still remains a high unmet need for new interventions to lower elevated IOP by targeting the TM, which is responsible for the majority of AH outflow.[2–4]

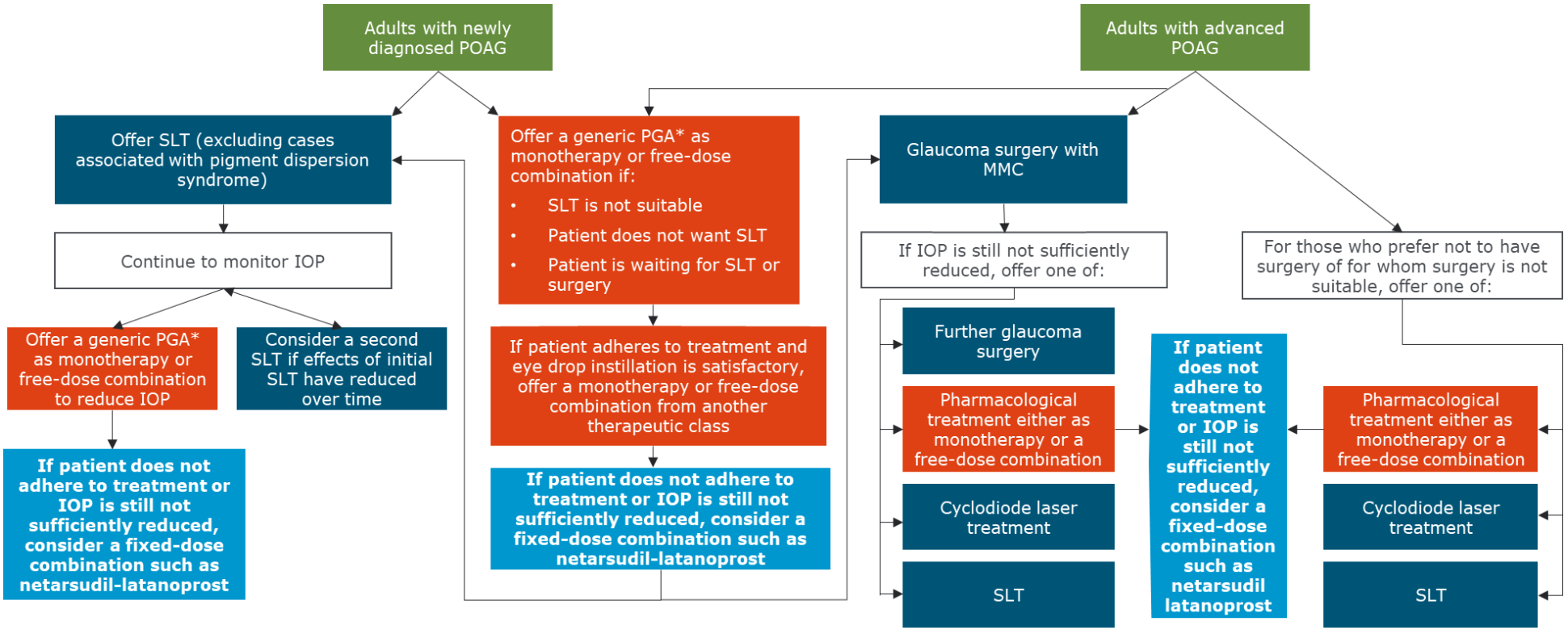
Anticipated positioning of netarsudil-latanoprost in the treatment pathway

Netarsudil-latanoprost is the first topical treatment to target the TM to increase AH outflow, thereby reducing pressure in the eye. Netarsudil lowers IOP by increasing the trabecular outflow which complements the increased uveoscleral outflow by latanoprost.[1] The fact that it is a FDC is also a benefit, as it is well known that FDCs not only improve adherence by reducing the medication burden, but also decrease the total amount of potentially delirious preservatives an eye is exposed to compared to free combination therapies.[49]

The addition of netarsudil-latanoprost in England will make a significant and substantial impact to the existing treatment pathways for POAG and OHT, as these have typically relied on the same classes of interventions for more than two decades.[50] Netarsudil-latanoprost will provide patients with a new and unique option to achieve their target IOP reduction. It is administered as one drop in the affected eye(s) once daily in the evening, which will support patient adherence to treatment.

Netarsudil-latanoprost will fit into the existing treatment pathways for POAG and OHT at the point where patients need to step up from PGA and/or topical monotherapy onto a FDC therapy to control IOP, in line with its marketing authorisation.[1] Netarsudil-latanoprost will also be available for patients who have previously been treated with free combination therapies, in instances where IOP has not been sufficiently reduced, or when patients present with adherence problems. FDC therapies, when available, are preferable to multiple topical treatments, which may reduce adherence and increase exposure to preservatives, according to EGS guidelines.[51] The anticipated positioning of netarsudil-latanoprost in England is summarised in Figure 6 for POAG, and Figure 7 for OHT.

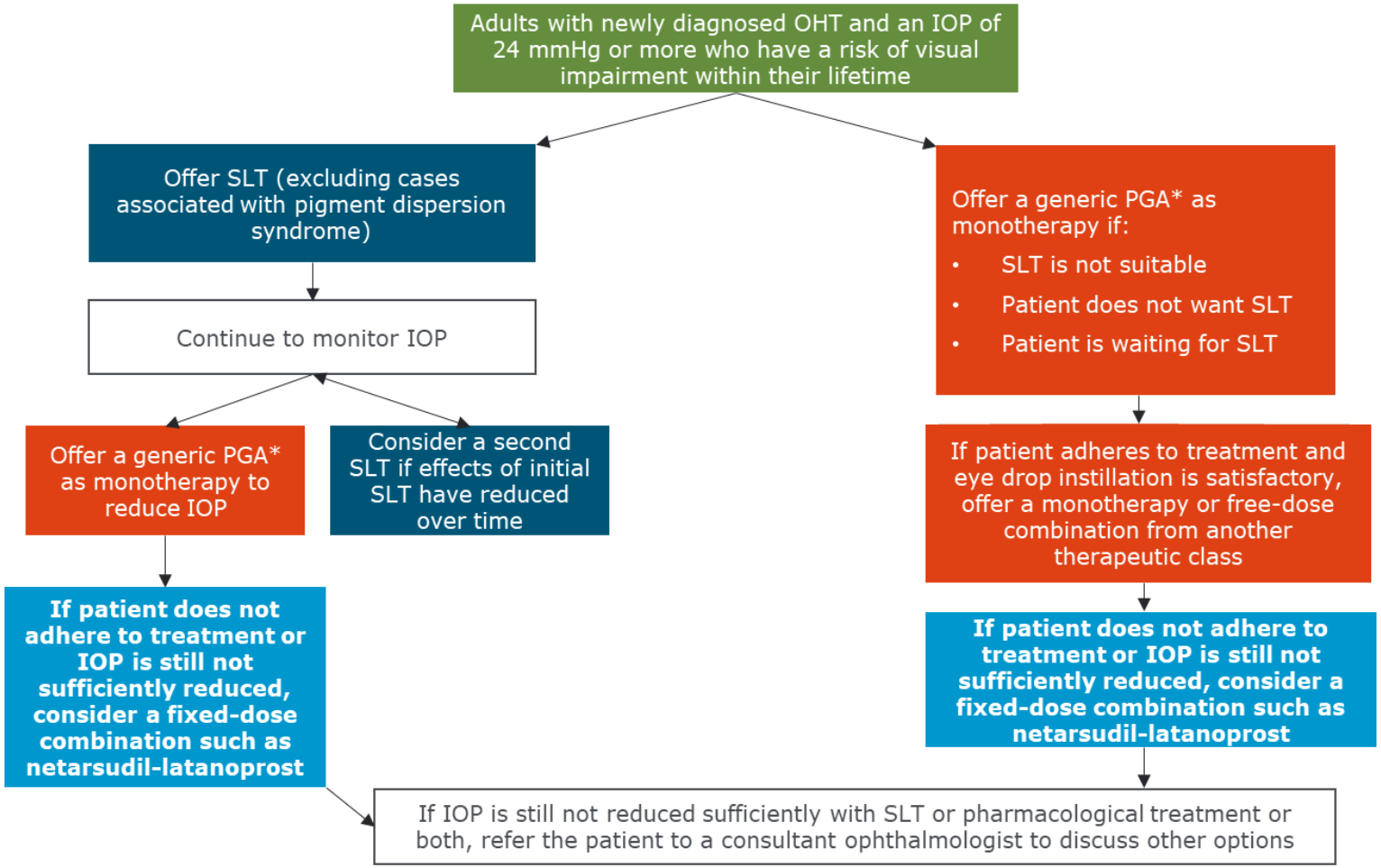
Figure 6: Anticipated positioning of netarsudil-latanoprost in patients with POAG



*For patients who cannot tolerate a pharmacological treatment, a monotherapy or free-dose combination treatment from a different class can be considered such as a BB, CAI, or sympathomimetic. Alternatively, preservative-free eye drops can be used if there is evidence that the person is allergic to the preservative or has clinically significant and symptomatic ocular surface disease.

Abbreviations: BB – Beta blocker; CAI – Carbonic anhydrase inhibitor; IOP – Intraocular pressure; MMC – Mitomycin C; PGA – Prostaglandin analogue; POAG – Primary open-angle glaucoma; SLT – Selective laser trabeculoplasty

Figure 7: Anticipated positioning of netarsudil-latanoprost in patients with OHT



*If a patient cannot tolerate their current treatment, offer an alternative generic PGA. If that is not tolerated, offer a BB. If neither of these options are tolerated, offer a non-generic PGA, a CAI, a sympathomimetic, a miotic, or a combination of treatments. Alternatively, preservative-free eye drops can be used if there is evidence that the person is allergic to the preservative or has clinically significant and symptomatic ocular surface disease.

Abbreviations: BB – Beta blocker; CAI – Carbonic anhydrase inhibitor; IOP – Intraocular pressure; OHT – Ocular hypertension; PGA – Prostaglandin analogue; SLT – Selective laser trabeculoplasty

B.1.4 Equality considerations

Glaucoma risk differs between ethnic groups.[52] There is not sufficient evidence to support separate evaluations of the clinical effectiveness and cost-effectiveness of netarsudil-latanoprost for separate ethnic groups.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted in November 2022 to identify clinical evidence for adult patients with POAG or OHT. See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

The evidence base of netarsudil-latanoprost (latanoprost 0.005% ophthalmic solution and netarsudil mesylate 0.02%) for reducing elevated IOP in adult patients with POAG or OHT for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction is provided in MERCURY 3, a phase III, double-blind, randomised controlled trial that enrolled approximately 440 patients (Table 3).[53]

Table 3: Clinical effectiveness evidence for netarsudil-latanoprost

Study	MERCURY 3 (NCT03284853)
Trial design	Prospective, double-blind, randomised (1:1), multicentre, active-controlled, parallel-group safety and efficacy trial, with a treatment and follow-up period of 180 days (six months)
Population	Adults (aged 18 years or older) with a diagnosis of open-angle glaucoma (OAG) or OHT in both eyes (a diagnosis of OAG in one eye and OHT in the fellow eye was acceptable), medicated IOP ≥17 mmHg in at least one eye and <28 mmHg in both eyes at the screening visit. • Number of patients *planned* recruited receiving: – Netarsudil-latanoprost (n=220) – Bimatoprost-timolol (n=220) • Number of patients *analysed* receiving: – Netarsudil-latanoprost (n=218) – Bimatoprost-timolol (n=212)
Intervention(s)	Latanoprost 0.005% ophthalmic solution and netarsudil mesylate 0.02%, taken as one drop in the affected eye(s) once daily in the evening; Alternative names: netarsudil-latanoprost, Roclanda, PG324
Comparator(s)	Bimatoprost 0.03% and timolol maleate 0.5% ophthalmic solution, taken as one drop in the affected eye(s) once daily, administered either in the morning or in the evening; Alternative names: bimatoprost-timolol, Ganfort
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale for use/non-use in the model	This study investigated netarsudil-latanoprost in the population to be treated as per the licensed indication, included a relevant comparator and includes key outcomes used in the economic model

Reported outcomes specified in the decision problem	*Primary endpoint:* • **Mean IOP within a treatment group at the following time points: 08:00, 10:00, and 16:00 hours at the week 2, week 6, and month 3 study visits** *Secondary endpoints:* • **Mean diurnal IOP within a treatment group at each post-treatment visit** • Mean change from diurnally adjusted baseline IOP at each post-treatment time point • Mean change from baseline in diurnal IOP at each post-treatment visit • Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point • Mean percent change from baseline in diurnal IOP at each post-treatment visit • Percentages of subjects achieving pre-specified mean, mean change, and percent mean change in diurnal IOP levels *Safety endpoints:* • **Adverse events (AEs)** • Heart rate and blood pressure • Biomicroscopy of anterior segment including evaluation of cornea, conjunctiva and anterior chamber • Dilated ophthalmoscopy • Best Corrected ETDRS Visual Acuity • Visual fields • Pachymetry • IOP • Clinical chemistry and haematology laboratory findings • Pregnancy testing (for women of childbearing potential) • Change in Self-Administered NEI Visual Functioning Questionnaire-25 (VFQ) score from baseline to study exit • **Change in Self-Administered Short Form Health Survey Questionnaire 36 (SF-36 V.2) score from baseline to study exit**
All other reported outcomes	N/A

Abbreviations: AE – Adverse event; ETDRS – Early Treatment Diabetic Retinopathy Study; IOP – Intraocular pressure; logMAR – logarithm of the minimum angle resolvable; mmHg – Millimetres of mercury; NEI – National Eye Institute; OAG – Open- angle glaucoma; OHT – Ocular hypertension; SF-36 – Self-Administered Short Form Health Survey Questionnaire 36; VFQ – Visual Functioning Questionnaire

In addition, netarsudil-latanoprost has been studied in two other phase III, double-blind, randomised controlled trials (RCTs): MERCURY 1 was a phase III double-blind, randomised parallel-group trial that investigated the efficacy and safety of a once daily FDC of netarsudil 0.02% and latanoprost 0.005%, compared with each active component, over a 12-month treatment period.[54] Similarly, MERCURY 2 was a phase III, double-blind, randomised superiority study that compared the ocular hypotensive efficacy and safety of a once daily FDC of netarsudil 0.02% and latanoprost 0.005%, compared with each active component, over a three-month treatment period.[54] Both MERCURY 1 and MERCURY 2 confirmed the

superiority of the FDC over the individual components.[55–57] In particular, there was a persistent reduction of IOP level with the FDC treatment during the two month post-study washout period which was not observed in the latanoprost only treatment group.[56]

It is expected that the NICE-recommended population for netarsudil-latanoprost will reflect the license wording and be limited to the reduction of elevated IOP in adult patients with POAG or OHT for whom monotherapy with a PGA or netarsudil provides insufficient IOP reduction (i.e., those eligible for FDCs).[58] As such, the MERCURY 1 and MERCURY 2 trials are not considered further in this submission since they compared netarsudil-latanoprost to monotherapies (netarsudil and latanoprost) rather than to FDCs.[58]

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 MERCURY 3 trial methodology

MERCURY 3 was a phase III, prospective, double-blind, randomised, multicentre, active-controlled, parallel-group study conducted in subjects who were ≥18 years of age, with elevated IOP and a diagnosis of OAG or OHT.[53] The study was conducted between September 2017 (actual study start date) and November 2020 (actual primary completion) at 68 sites across 11 countries (Austria, Belgium, Czechia, France, Germany, Hungary, Italy, Latvia, Poland, Spain and the UK).[59]

Originally, 440 subjects were planned to be enrolled. However, an administrative decision was made to stop screening activities when the study was >90% enrolled. Therefore, a total of 430 subjects were enrolled and randomised in the study (218 in the netarsudil-latanoprost group and 212 in the bimatoprost-timolol group). The study duration for enrolled subjects was 180 days from visit 1 (screening) to the last visit (visit 9 [day 180 ± 7 days]). Visit 1 (screening) occurred up to approximately four weeks before visit 2 (qualification visit #1); the duration between visit 1 and visit 2 varied depending on the washout period required for the prior ocular hypotensive medication (Table 4).

Table 4: Ocular hypotensive medication washout period in MERCURY 3[53]

Medication class	Minimum washout period
Prostaglandin analogues	4 weeks
β-adrenoceptor antagonists	4 weeks
Adrenergic agonists (including α-agonists such as brimonidine and apraclonidine)	2 weeks
Muscarinic agonists (e.g., pilocarpine), Carbonic anhydrase inhibitors (topical or oral)	5 days

Eligible patients were enrolled and randomly assigned according to a randomisation code (prepared by an independent biostatistician) at visit 3 (qualification visit #2). Patients were randomly assigned to one of two treatment groups at a 1:1 ratio to netarsudil-latanoprost or bimatoprost-timolol. Netarsudil-latanoprost and bimatoprost-timolol were each administered as a single drop in both eyes once daily (QD) in the evening (between 20:00 and 22:00). The patients, investigators, clinical study team and personnel involved in day-to-day study management were blinded to treatment assignments. Additionally, to minimise unmasking due

to the differences in bottle closure cap colour between the two treatments, clinical supplies were packaged in identical outer containers labelled appropriately for clinical trial use.

Randomisation was stratified by investigative site and maximum baseline IOP <25 mmHg vs. ≥25 mmHg. The follow-up duration of the trial was six months (finalised at visit 9, day 180 [± 7 days]) and the treatment period lasted for the study duration. The first three months of the study were used to evaluate the primary efficacy endpoint; the subsequent three months focussed primarily on safety endpoints and included IOP measurements at 10:00 hours.

The primary efficacy endpoint was mean IOP within each treatment group at the following time points: 08:00, 10:00 and 16:00 hours at the week 2, week 6 and month 3 study visits.

Secondary efficacy endpoints included:

- Mean diurnal IOP within each treatment group at each post-treatment visit
- Mean change from diurnally adjusted baseline IOP at each post-treatment time point
- Mean change from baseline in diurnal IOP at each post-treatment visit
- Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point
- Mean percent change from baseline in diurnal IOP at each post-treatment visit
- Percentage of subjects achieving pre-specified mean, mean change and percent mean change in diurnal IOP levels

The primary safety measurements were visual acuity, goniometry, pachymetry, objective biomicroscopic and ophthalmoscopic examination and monitoring of AEs.

Other safety measures included:

- Systemic safety measures: pregnancy testing, heart rate, blood pressure and clinical laboratory evaluations
- Change in self-administered NEI VFQ-25, and SF-36 (version 2) scores from baseline to study exit

A summary of the study design and methodology is reported in Table 5.

Table 5: MERCURY 3 study design and methodology

Study	MERCURY 3 (NCT03284853)[53]
Trial design	Prospective, double-blind, randomised (1:1), multicentre, active-controlled, parallel-group safety and efficacy trial, with a treatment period of 180 days (six months). The first three months were used to evaluate the primary efficacy endpoint; the subsequent three months focussed primarily on safety endpoints and included IOP measurements at 10:00 hours.
Eligibility criteria	**Inclusion criteria** Patients were eligible for inclusion in the study if they met the following criteria: • Must be 18 years of age or older • Diagnosis of OAG or OHT in both eyes (OAG in one eye and OHT in the fellow eye was acceptable) • Subjects insufficiently controlled and/or subjects considered in need for combination therapy by the investigators • Medicated IOP ≥17 mmHg in at least one eye and <28 mmHg in both eyes at screening visit

	• Unmedicated (post-washout) IOP >20 mmHg in at least one eye and <36 mmHg in both eyes at two qualification visits at 08:00, 2-7 days apart. At the second qualification visit, have IOP >17 mmHg in at least one eye and <36 mmHg in both eyes at 10:00 and 16:00. Note: For purposes of determining eligibility of subjects to be enrolled, the non-integral IOP mean number was used. Any non-integral mean IOP number was not rounded. If only one eye qualified at the second qualification visit, it must have been the same eye that qualified on the first visit and this was the study eye for the duration of the study • Best corrected visual acuity +1.0 Logarithm of the Minimum Angle of Resolution (logMAR) or better by ETDRS in each eye (equivalent to 20/200 or better Snellen visual acuity in each eye) • Able and willing to give signed informed consent and follow study instructions • Women needed to be either of non-childbearing potential, or women with childbearing potential and men with reproductive potential needed to be willing to practice acceptable methods of birth control during the study • Women of childbearing potential needed to have a negative urine pregnancy test within seven days of first dose of study treatment and agreed to use highly effective contraception during the study and for three months after the last dose of study medication • Men that had a female partner of childbearing potential needed to have either had a prior vasectomy or agreed to use an effective form of contraception from time of randomisation and for three months following the last dose of study medication • In France, a subject was eligible for inclusion in this study only if either affiliated to or as a beneficiary of a social security number **Exclusion criteria** Patients were to be excluded from the study if they met any of the following criteria: *Ophthalmic:* • Clinically significant ocular disease (e.g., corneal oedema, uveitis, or severe keratoconjunctivitis sicca) which might have interfered with interpretation of the study efficacy endpoints or with safety assessments, including subjects with glaucomatous damage so severe that washout of ocular hypotensive medications for four weeks or longer if needed, was not judged safe as it would put the subject at risk for further vision loss • Pseudo exfoliation or pigment dispersion component glaucoma, history of angle closure glaucoma, or narrow angles i.e. Grade 2 Shaffer (Chan 1981) or less extreme narrow angle with complete or partial closure. Note: previous laser peripheral iridotomy was not acceptable • IOP ≥36 mmHg (unmedicated) in either eye (individuals who were excluded for this criterion were not allowed to attempt requalification), or use of more than two ocular hypotensive medications within 30 days of screening. Note: FDC medications, for the purpose of this exclusion criterion, counted as one medication. However, subjects that were currently taking two FDC products were excluded • Treatment naïve subjects • Prior treatment with bimatoprost-timolol topical eye drops where the subject's IOP did not achieve the target IOP and was considered either a therapeutic failure or to have insufficient response. Subjects that were currently (immediately prior to screening visit) being treated with bimatoprost-timolol were excluded from the study • Known hypersensitivity to any component of the investigational formulations used (e.g., benzalkonium chloride) or to fluorescein

	• Previous glaucoma intraocular surgery, including SLT or argon laser trabeculoplasty (ALT) in either eye • Refractive surgery in either eye (e.g., radial keratotomy, photorefractive keratectomy (PPK), laser-assisted in situ keratomileusis (LASIK), corneal cross-linking, keratoplasty) • Ocular trauma within the six months prior to screening, or ocular surgery or non-refractive laser treatment within three months prior to screening • Recent or current evidence of ocular infection or inflammation in either eye • Current evidence of clinically significant blepharitis, conjunctivitis, keratitis • Current evidence or history of herpes simplex or zoster keratitis in either eye at screening • Use of ocular medication in either eye of any kind within 30 days of screening and throughout the study, with the exception of a) ocular hypotensive medications which must have been the same medication for 30 days prior to screening (which must be washed out according to the provided schedule), b) lid scrubs (which may be used prior to, but not after, screening), c) lubricating drops for dry eye (which may be used throughout the study), as prescribed by the investigator • Mean central corneal thickness greater than 620 µm at screening • Any abnormality preventing reliable Goldmann applanation tonometry of either eye (e.g., keratoconus) *Systemic:* • Clinically significant abnormalities in laboratory tests at screening • Known hypersensitivity or contraindication to bimatoprost-timolol and to β-adrenoceptor antagonists (e.g. chronic obstructive pulmonary disease or bronchial asthma; abnormally low blood pressure or heart rate; second or third-degree heart block or congestive heart failure, cardiac failure, cardiac shock and severe diabetes) • Clinically significant systemic disease which might have interfered with the study • Participation in any investigational study within 30 days prior to screening • Systemic medication including corticosteroid containing drugs that could have had a substantial effect on IOP which had not been maintained at a consistent dose and regime within 30 days prior to screening, and were anticipated to change in dose and/or regime during the study • Use of topical steroid containing medications on the face or in or around the eyes • Women of childbearing potential who were pregnant, nursing, planning a pregnancy, or not using a medically acceptable and highly effective form of birth control. An adult woman was considered to be of childbearing potential unless she was one year post-menopausal (one year without menses with appropriate clinical profile, e.g. age appropriate, >45 years in the absence of hormone replacement therapy (HRT). In questionable cases the subject must have had follicle-stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40 pg/mL (<140 pmol/L)) or three months post-surgical sterilisation • Vulnerable subjects such as minors, adults under legal protection or unable to express their consent (e.g. hospitalised persons in a coma), persons deprived of liberty (prisoners from jails), or persons subject to psychiatric case
Settings and location where data were collected	68 participating secondary care outpatient sites in 11 countries (Austria, Belgium, Czechia, France, Germany, Hungary, Italy, Latvia, Poland, Spain, UK)

Study duration	05 September 2017 - 06 November 2020
Trial drugs and concomitant medications	*Trial drugs:* • Netarsudil 0.02% and latanoprost 0.005% ophthalmic solution, QD • Bimatoprost 0.03% and timolol maleate 0.5% ophthalmic solution, QD Subjects instilled one drop of study drug into each eye, one time per day in the evening between 20:00 and 22:00 (including days when the subject was scheduled to visit the study site) *Permitted concomitant medications:* • Over-the-counter (OTC) artificial tear lubricant products, with a minimum of 10 minutes between OTC products and study medication • Systemic therapy with agents including corticosteroids that could influence IOP (needed to be consistent in dose, regimen, and agent with the 30 days prior to screening and throughout the study) • Intermittent topical steroids for certain skin conditions (but not on the face) • Contact lenses
Outcomes used in the economic model or specified in the scope, including primary outcome	*Primary endpoint:* • **Mean IOP within a treatment group at the following time points: 08:00, 10:00, and 16:00 hours at the week 2, week 6, and month 3 study visits** *Secondary endpoints:* • **Mean diurnal IOP within a treatment group at each post-treatment visit** • Mean change from diurnally adjusted baseline IOP at each post-treatment time point • Mean change from baseline in diurnal IOP at each post-treatment visit • Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point • Mean percent change from baseline in diurnal IOP at each post-treatment visit • Percentage of subjects achieving pre-specified mean, mean change, and percent mean change in diurnal IOP levels *Safety endpoints:* • **AEs** • Heart rate and blood pressure • Biomicroscopy of anterior segment including evaluation of cornea, conjunctiva and anterior chamber • Dilated ophthalmoscopy • Best Corrected ETDRS Visual Acuity • Visual fields • Pachymetry • Clinical chemistry and haematology laboratory findings • Pregnancy testing (for women of childbearing potential) • Change in Self-Administered NEI Visual Functioning Questionnaire-25 (VFQ) score from baseline to study exit • **Change in Self-Administered Short Form Health Survey Questionnaire 36 (SF-36 V.2) score from baseline to study exit**

Abbreviations: AE – Adverse event; ALT – Argon laser trabeculoplasty; ETDRS – Early Treatment Diabetic Retinopathy Study; FSH – Follicle-stimulating hormone; HRT – Hormone replacement therapy; IOP – Intraocular

pressure; L – Litre; logMAR – Logarithm of the Minimum Angle of Resolution; mIU – Milli-international units; mL – Millilitres; mmHg – Millimetres of mercury; NEI – National Eye Institute; OAG – Open-angle glaucoma; OHT – Ocular hypertension; OTC – Over-the-counter; Pg – Picogram; Pmol – Picomole; PRK – Photorefractive keratectomy; QD – Once daily; SF-36 – Self-administered Short Form Health Survey Questionnaire; SLT – Selective laser trabeculectomy; VFQ – Visual Functioning Questionnaire; µm – Micrometres

B.2.3.2 Baseline characteristics of the MERCURY 3 trial

A total of 430 patients were enrolled in the intention-to-treat (ITT) population of MERCURY 3, with 218 and 212 patients randomly assigned to receive treatment once daily with netarsudil-latanoprost or bimatoprost-timolol, respectively.[53]

Between treatment groups, the demographic characteristics were similar except for sex. In the netarsudil-latanoprost group, fewer subjects were male (39.9%) compared to the bimatoprost-timolol group (56.6%). Treatment effect modifiers and prognostic variables were validated with a UK clinical expert, described in further detail in section B.2.9.2.3. However, they did not consider sex to be a treatment effect modifier or prognostic variable, therefore the difference in sex demographics between the two treatment arms of MERCURY 3 is not expected to bias results. The mean age ranged between 67.0 (bimatoprost-timolol group) and 67.3 (netarsudil-latanoprost group) years across treatment arms, and the majority of patients were Caucasian, with 96.3% and 94.3% in the netarsudil-latanoprost and bimatoprost-timolol groups, respectively. A similar proportion of patients in each treatment arm were Hispanic or Latino – 28.0% and 26.4% of patients were Hispanic or Latino in the netarsudil-latanoprost and bimatoprost-timolol groups, respectively.

Between the treatment groups, the disease-relevant characteristics were similar except for differences in prior prostaglandin therapy. In the netarsudil-latanoprost group, more subjects had received prior prostaglandin therapy (78.4%) compared to the bimatoprost-timolol group (69.3%). However, prior treatment was not validated as a key effect modifier or prognostic variable by a UK clinical expert and therefore, the difference in prior treatment demographics between the two treatment arms of MERCURY 3 is not expected to bias results.

Except for sex and prior prostaglandin therapy, baseline characteristics were considered similar between the netarsudil-latanoprost and bimatoprost-timolol groups, denoting a randomisation process that produced an appropriate balance of known or unknown prognostic factors, baseline conditions, or prior hypotensive treatments.

A summary of subject demographics and baseline characteristics in the ITT population of the MERCURY 3 trial is reported in Table 7.[6]

Table 7: Baseline characteristics in MERCURY 3: ITT population (N=430)[53]

	Netarsudil-latanoprost QD (n=218)	Bimatoprost-timolol QD (n=212)
Demographic characteristics		
Sex		
Male – n (%)	87 (39.9)	120 (56.6)
Female – n (%)	131 (60.1)	92 (43.4)
Age (years)		
Mean (SD)	67.3 (12.03)	67.0 (11.27)

Median (min-max)	69.0 (25-91)	68.5 (22-91)
<65 – n (%)	71 (32.6)	79 (37.3)
≥65 – n (%)	147 (67.4)	133 (62.7)
Race		
Caucasian – n (%)	210 (96.3)	200 (94.3)
Asian – n (%)	0 (0.0)	3 (1.4)
Black or African American – n (%)	4 (1.8)	5 (2.4)
Native American – n (%)	[redacted]	[redacted]
Other– n (%)	[redacted]	[redacted]
Not applicable* – n (%)	[redacted]	[redacted]
Ethnicity		
Hispanic or Latino – n (%)	61 (28.0)	56 (26.4)
Not Hispanic or Latino – n (%)	157 (72.0)	156 (73.6)
Disease-relevant baseline characteristics		
Iris colour – study eye		
Blue/Grey/Green – n (%)	[redacted]	[redacted]
Brown/Black – n (%)	[redacted]	[redacted]
Hazel – n (%)	[redacted]	[redacted]
Other – n (%)	[redacted]	[redacted]
Study eye diagnosis		
OHT – n (%)	94 (43.1)	100 (47.2)
OAG – n (%)	124 (56.9)	112 (52.8)
Time since current diagnosis (weeks)		
Mean (SD)	[redacted]	[redacted]
Median (min-max)	[redacted]	[redacted]
Prior hypotensive therapy		
Combination therapy – n (%)	[redacted]	[redacted]
Prostaglandins (monotherapy) – n (%)	[redacted]	[redacted]
Others (monotherapy) – n (%)	[redacted]	[redacted]
Prior prostaglandin therapy – n (%)	171 (78.4)	147 (69.3)
No prior prostaglandin Therapy – n (%)	47 (21.6)	65 (30.7)
Time on current hypotensive therapy		
Mean (SD)	[redacted]	[redacted]
Median (min-max)	[redacted]	[redacted]
IOP (mmHg) at screening – study eye		
Mean (SD)	[redacted]	[redacted]

Median (min-max)	[redacted]	[redacted]
Mean diurnal IOP (mmHg) on day 1 – study eye		
Mean (SD)	25.05 (3.41)	24.81 (3.26)
Median	[redacted]	[redacted]

Abbreviations: IOP – Intraocular pressure; ITT – Intention-to-treat; mmHg – Millimetres of mercury; OAG – Open-angle glaucoma; OHT – Ocular hypertension; QD – Once daily; SD – Standard deviation
*Participants that were unwilling to disclose their ethnicity.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Details on the number of participants eligible to enter the MERCURY 3 trial are provided in Appendix D.

Table 8 shows the details of the statistical analyses conducted for the MERCURY 3 trial.

Table 8: MERCURY 3 statistical analysis

Trial number (acronym)	MERCURY 3 (NCT03284853)[53]
Hypothesis objective	The primary hypotheses were: • H_0: The difference between study eyes treated with netarsudil-latanoprost and study eyes treated with bimatoprost-timolol, in mean IOP at the following time points: 08:00, 10:00 and 16:00 hours at the week 2, week 6 and month 3 visits, is >1.5 mmHg for at least one time point over all visits, or is >1.0 mmHg for a majority of time points over all visits. • H_1: The difference between study eyes treated with netarsudil-latanoprost and study eyes treated with bimatoprost-timolol, in mean IOP at the following time points: 08:00, 10:00 and 16:00 hours at the week 2, week 6 and month 3 visits, is ≤1.5 mmHg for all visits and is ≤1.0 mmHg for the majority of time points (six out of nine) over all visits.
Sample size, power calculation	Assuming no difference between netarsudil-latanoprost and bimatoprost-timolol, a two-tailed alpha of 0.05 (2-sided 95% CI) at each of the nine time points, a common SD of 3.5 mmHg, and a correlation between time points of 0.60 or less, it was estimated that 200 ITT subjects per arm were necessary to have 85% power to show clinical non-inferiority of netarsudil-latanoprost to bimatoprost-timolol in the mean change from baseline in IOP. To account for the potential of additional variability in the primary efficacy outcome due to multiple imputations of missing data, up to 220 subjects per arm were planned to be randomised.
Outcome populations	Three populations were defined in the study: • The ITT population was defined as all randomised subjects who received at least one dose of study medication. The ITT population was the primary population for efficacy analyses and used to summarise a subset of efficacy variables and summarise subjects as randomised. • The per-protocol (PP) population was defined as a subset of the ITT population, which included those subjects (and their visits) who did not have major protocol violations likely to seriously affect the primary outcome of the study, as judged by a masked evaluation prior to the unmasking of the study treatment. This population was the secondary population for efficacy analyses and was used to summarise all efficacy variables. If the PP and ITT populations were exactly the same, then it was planned that additional efficacy analyses on the PP population were not to be performed.

	• The safety population was defined as all randomised patients who received at least one dose of study medication. Patients were analysed for safety according to treatment received.
Statistical analysis	The MERCURY 3 trial assessed the primary efficacy outcome which was the comparison of netarsudil-latanoprost relative to bimatoprost-timolol for mean IOP within a treatment group at 08:00, 10:00, and 16:00 hours at the week 2, week 6, and month 3 visits. Mean diurnal IOP values were constructed by averaging the three IOP measurements on each of week 2, week 6, and month 3. Each subject had one eye designated as the study eye. Only study eyes were evaluated for all the efficacy measures. All statistical tests were performed at a 2-sided 5% significance level. The primary analysis of the primary outcome employed a linear model with IOP at the given visit and time point as the response, baseline IOP as a covariate and treatment as a main effect factor at each time point, using the ITT population with multiple imputation techniques to impute missing data. The least squares mean differences were presented as well as 2-sided 95% confidence intervals and p-values. Secondary analyses of the primary endpoint were completed using individual two-sample t-tests and 95% t-distribution confidence intervals for each comparison at each time point using the ITT and PP populations. Similar analyses were completed on the secondary endpoints. Subgroup analyses were performed based on pre-study characteristics. IOP was compared at each post-dose time point between treatment groups using an Analysis of Covariance (ANCOVA) model with treatment as the main effect, baseline IOP and subgroup as covariates, and the interaction of treatment by subgroup.
Data management, patient withdrawals	A total of 430 subjects were enrolled and a similar numbers of subjects were randomised in each treatment group (netarsudil-latanoprost n=218 vs. bimatoprost-timolol n=212). Whilst 440 subjects were planned to be enrolled, an administrative decision was made to stop screening activities when the study was >90% enrolled. The primary efficacy analysis population was changed from PP to ITT, and consequently the sample size was reduced from a total of 472 to up to 220 subjects per arm (approximately 440 subjects in total). Among subjects who terminated the study early, the most common reasons overall were: • Adverse event: 18.3% (40/218) and 1.9% (4/212) in the netarsudil-latanoprost and bimatoprost-timolol groups, respectively • Withdrawal of consent: 2.3% (5/218) and 0.5% (1/212) in the netarsudil-latanoprost and bimatoprost-timolol groups, respectively *See section B.1.1 for a breakdown of the adverse event rates.*
Interim analyses	An interim analysis was planned when all subjects had completed at least three months of treatment (primary efficacy endpoint). The study report included the final analysis of the primary efficacy and safety data collected through the extension period up to six months. When all subjects had completed three months of treatment, the study was unmasked to analyse the 3-month efficacy and safety data. The interim analysis was completed at an overall 2-sided alpha of 0.05 (5%) significance level.

Abbreviations: CI – Confidence interval; IOP – Intraocular pressure; ITT – Intention-to-treat; PP – Per-protocol; SD – Standard deviation.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

A complete quality assessment for the MERCURY 3 trial and the remaining RCTs extracted in the clinical SLR, is provided in Appendix D.

B.2.6 Clinical effectiveness results of the MERCURY 3 trial

B.2.6.1 Primary efficacy endpoint: mean IOP at specified time points at week 2, week 6 and month 3 – ITT population

The primary efficacy endpoint in the MERCURY 3 trial was the comparison of netarsudil-latanoprost to bimatoprost-timolol for the mean IOP at specified time points at week 2, week 6 and month 3.[53] Table 9 displays the mean IOP at specified time points at week 2, week 6, and month 3 for the ITT population, with imputation by Markov Chain Monte Carlo (MCMC) techniques. The criteria for clinical non-inferiority was the upper limit of the 95% CIs around the difference between netarsudil-latanoprost and bimatoprost-timolol being ≤1.5 mmHg at all time points, and ≤1.0 mmHg at most time points through to month 3.

The clinical non-inferiority of netarsudil-latanoprost relative to bimatoprost-timolol in the ITT population was demonstrated with the upper limit of the 95% CIs around the difference being ≤1.5 mmHg at all time points, and ≤1.0 mmHg at the majority (6 out of 9) of time points from week 2 through month 3.

The least square mean IOP ranged from [redacted] to [redacted] mmHg for study eyes treated with netarsudil-latanoprost across all time points through to month 3. For study eyes treated with bimatoprost-timolol, the least square mean IOP ranged from [redacted] to [redacted] mmHg. The differences between the least square mean of the two arms ranged from -0.48 to 0.88, with a statistically significant improvement at the 95% confidence level observed for the netarsudil-latanoprost arm in 2/9 time points.

Table 9: MERCURY 3 baseline-adjusted ANCOVAs for study eye IOP (mmHg) at each post-dose time point - ITT population with MCMC

	Netarsudil-latanoprost QD (N=218)	Bimatoprost-timolol QD (N=212)	Difference from bimatoprost-timolol
Week 2 (day 15), 08:00 hours			
n	218	212	-
LS mean (p-value)	[redacted]	[redacted]	0.17 (0.5581)
SE [95% 2-sided CI]	[redacted]	[redacted]	0.29 [0.40, 0.74]
Week 2 (day 15), 10:00 hours			
n	218	212	-
LS mean (p-value)	[redacted]	[redacted]	-0.17 (0.5193)
SE [95% 2-sided CI]	[redacted]	[redacted]	0.27 [-0.70, 0.35]
Week 2 (day 15), 16:00 hours			
n	218	212	-
LS mean (p-value)	[redacted]	[redacted]	-0.48 (0.0904)
SE [95% 2-sided CI]	[redacted]	[redacted]	0.28 [-1.03, 0.08]

	Netarsudil-latanoprost QD (N=218)	Bimatoprost-timolol QD (N=212)	Difference from bimatoprost-timolol
Week 6 (day 43), 08:00 hours			
n	218	212	-
LS mean (p-value)	[redacted]	[redacted]	0.88 (0.0023)**
SE [95% 2-sided CI]	[redacted]	[redacted]	0.29 [-0.32, 1.44]
Week 6 (day 43), 10:00 hours			
n	218	212	-
LS mean (p-value)	[redacted]	[redacted]	0.40 (0.1510)
SE [95% 2-sided CI]	[redacted]	[redacted]	0.28 [-0.15, 0.94]
Week 6 (day 43), 16:00 hours			
n	218	212	-
LS mean (p-value)	[redacted]	[redacted]	-0.08 (0.7613)
SE [95% 2-sided CI]	[redacted]	[redacted]	0.28 [-0.63, 0.46]
Month 3 (day 90), 08:00 hours			
n	218	212	-
LS mean (p-value)	[redacted]	[redacted]	0.66 (0.0163)*
SE [95% 2-sided CI]	[redacted]	[redacted]	0.28 [0.12, 1.20]
Month 3 (day 90), 10:00 hours			
n	218	212	-
LS mean (p-value)	[redacted]	[redacted]	0.42 (0.1706)
SE [95% 2-sided CI]	[redacted]	[redacted]	0.31 [-0.18, 1.03]
Month 3 (day 90), 16:00 hours			
n	218	212	-
LS mean (p-value)	[redacted]	[redacted]	0.19 (0.5126)
SE [95% 2-sided CI]	[redacted]	[redacted]	0.29 [-0.38, 0.76]

Source: MERCURY 3 CSR[53]

Abbreviations: CI – Confidence interval; IOP – Intraocular pressure; ITT – Intention-to-treat; MCMC – Markov Chain Monte Carlo; mmHg – Millimetres of mercury; QD – Once Daily; LS – Least square; SE – Standard error

*p-value <0.05; **p-value <0.01; ***p-value <0.001.

The ANCOVA model has treatment as a factor and baseline as a covariate. Difference from bimatoprost-timolol, SE of the difference, 2-sided CIs, and p-values are based on an ANCOVA comparing netarsudil-latanoprost QD with bimatoprost-timolol QD.

Sensitivity analyses of the primary endpoint were conducted to assess for clinical non-inferiority of netarsudil-latanoprost relative to bimatoprost-timolol when imputing the primary analysis model with observed values, last observation carried forward (LOCF) and baseline observation carried forward (BOCF). Results of the sensitivity analysis are summarised in Table 10. Analyses using observed values were generally consistent with the primary analyses, i.e., clinical non-inferiority was demonstrated for netarsudil-latanoprost relative to bimatoprost-timolol. For the sensitivity analyses using LOCF and BOCF methods, the threshold for clinical non-inferiority (a between-group difference of ≤1.5 mmHg) was demonstrated at week 2 but not at week 6 or month 3.

Table 10: MERCURY 3 baseline-adjusted ANCOVAs for study eye IOP (mmHg) sensitivity analyses summary

Analysis populations	Imputation	Non-inferiority of netarsudil-latanoprost relative to bimatoprost-timolol achieved?	Clinical significance in the difference between LS mean IOP of treatment arms*
ITT	MCMC	[redacted]	[redacted]
	Observed	[redacted]	[redacted]
	LOCF	[redacted]	[redacted]
	BOCF	[redacted]	[redacted]

Source: MERCURY 3 CSR[53]

Abbreviations: BOCF – Baseline observation carried forward; IOP – Intraocular pressure; ITT – Intention-to-treat; MCMC – Markov Chain Monte Carlo; mmHg – Millimetres of mercury; LOCF – Last observation carried forward; LS – Least square

*Tests included LS mean IOP of netarsudil-latanoprost relative to bimatoprost-timolol at three time points for visit 4, 5, and 6. Only the maximum level of significance recorded.

B.2.6.2 Secondary efficacy endpoint: mean diurnal IOP within a treatment group at each post-treatment visit – ITT population

Table 11 shows the least square mean diurnal IOP (constructed by averaging the three IOP values collected during a single visit day, i.e., at 08:00, 10:00, and 16:00 hours) at week 2, week 6, and month 3 for the ITT population, with imputation by MCMC.

The post-treatment mean diurnal IOPs ranged from 15.39 to 15.64 mmHg for the netarsudil-latanoprost group, and 15.19 to 15.56 mmHg for the bimatoprost-timolol group. There was no evidence of a statistically significant difference in mean diurnal IOP between the two groups.

The clinical non-inferiority of netarsudil-latanoprost relative to bimatoprost-timolol in the ITT population was demonstrated with the upper limit of the 95% CIs around the difference being ≤1.0 mmHg at all three time points from week 2 through month 3.

The differences between the least square mean of the two arms ranged from [redacted] to [redacted], with statistically significant improvements at the 95% confidence level not observed for any of the time points.

Table 11: MERCURY 3 baseline-adjusted ANCOVAs for study eye mean diurnal IOP (mmHg) at post-dose visit - ITT population with MCMC

	Netarsudil-latanoprost QD (N=218)	Bimatoprost-timolol QD (N=212)	Difference from bimatoprost-timolol
Week 2 (day 15), diurnal mean			
n	218	212	-
LS mean (p-value)	15.39	15.56	[redacted]
SE [95% 2-sided CI]	[redacted]	[redacted]	[redacted]
Week 6 (day 43), diurnal mean			
n	218	212	-
LS mean (p-value)	15.64	15.25	[redacted]
SE [95% 2-sided CI]	[redacted]	[redacted]	[redacted]

Month 3 (day 90), diurnal mean			
n	218	212	-
LS mean (p-value)	15.61	15.19	[redacted]
SE [95% 2-sided CI]	[redacted]	[redacted]	[redacted]

Source: MERCURY 3 CSR[53]

Abbreviations: CI – Confidence interval; IOP – Intraocular pressure; ITT – Intention-to-treat; MCMC – Markov Chain Monte Carlo; mmHg – Millimetres of mercury; QD – Once daily; LS – Least square; SE – Standard error

*p-value <0.05; **p-value <0.01; ***p-value <0.001.

The ANCOVA model has treatment as a factor and baseline as a covariate. Difference from bimatoprost-timolol, SE of the difference, 2-sided CIs, and p-values are based on an ANCOVA comparing netarsudil-latanoprost QD with bimatoprost-timolol QD.

B.2.6.3 Secondary efficacy endpoint: actual mean and mean change from diurnally adjusted baseline IOP at each post-treatment time point – ITT population

Post-treatment mean IOPs ranged from [redacted] to [redacted] mmHg for the netarsudil-latanoprost group, and [redacted] to [redacted] mmHg for the bimatoprost-timolol group. The mean change from diurnally adjusted baseline in IOP ranged from -9.94 to -9.03 mmHg in the netarsudil-latanoprost group and -10.41 to -8.45 mmHg in the bimatoprost-timolol group across all time points. Netarsudil-latanoprost showed a consistent reduction in IOP throughout each time point.

Differences between the netarsudil-latanoprost and bimatoprost-timolol arm in actual IOP varied from [redacted] to [redacted], with a statistically significant difference at the 95% level in 2/9 of the time points.

B.2.6.4 Secondary efficacy endpoint: mean change from baseline in diurnal IOP at each post-treatment visit (MCMC) – ITT population

The mean diurnal IOP in the study eye at baseline was similar among both treatment groups, at 25.05 mmHg in the netarsudil-latanoprost group, and [redacted] mmHg in the bimatoprost-timolol group. Similar observations were made at week 6 ([redacted] mmHg and [redacted] mmHg) and week 12 ([redacted] mmHg and [redacted] mmHg).

Across the three time points, a similar change from baseline in mean diurnal IOP was observed in the netarsudil-latanoprost and bimatoprost-timolol groups. At week 6, this constituted [redacted] mmHg and [redacted] mmHg for netarsudil-latanoprost and bimatoprost-timolol respectively, and at week 12 constituted [redacted] mmHg and [redacted] mmHg in the respective groups. At both time points, there was no statistically significant difference observed between the two groups.

B.2.6.5 Secondary efficacy endpoint: mean percent change from diurnally adjusted baseline IOP at each post-treatment time point – ITT population

The mean IOP in the study eye was similar at baseline for both treatment groups (Table 12).

The mean percent change from diurnally adjusted baseline IOP was numerically greater in the bimatoprost-timolol group ([redacted] to [redacted]) compared to the netarsudil-latanoprost group ([redacted] to [redacted]) from week 2 to month 3. At the majority of time points, there was no statistically significant difference between the treatment groups.

Table 12: Mean percent change from baseline diurnally adjusted IOP in study eye at each post-dose time point (ITT population)

	Netarsudil-latanoprost QD (N=218)	Bimatoprost-timolol QD (N=212)
V4: day 15, 08:00 hours		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min	[redacted]	[redacted]
Max	[redacted]	[redacted]
Difference from bimatoprost-timolol	[redacted]	-
95% 2-sided CI	[redacted]	-
p-value	[redacted]	-
V4: day 15, 10:00 hours		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min	[redacted]	[redacted]
Max	[redacted]	[redacted]
Difference from bimatoprost-timolol	[redacted]	-
95% 2-sided CI	[redacted]	-
p-value	[redacted]	-
V4: day 15, 16:00 hours		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min	[redacted]	[redacted]
Max	[redacted]	[redacted]
Difference from bimatoprost-timolol	[redacted]	-
95% 2-sided CI	[redacted]	-
p-value	[redacted]	-
V4: day 15, diurnal mean		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]

	Netarsudil-latanoprost QD (N=218)	Bimatoprost-timolol QD (N=212)
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min	[redacted]	[redacted]
Max	[redacted]	[redacted]
Difference from bimatoprost-timolol	[redacted]	-
95% 2-sided CI	[redacted]	-
p-value	[redacted]	-
V5: day 43, 08:00 hours		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min	[redacted]	[redacted]
Max	[redacted]	[redacted]
Difference from bimatoprost-timolol	[redacted]	-
95% 2-sided CI	[redacted]	-
p-value	[redacted]	-
V5: day 43, 10:00 hours		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min	[redacted]	[redacted]
Max	[redacted]	[redacted]
Difference from bimatoprost-timolol	[redacted]	-
95% 2-sided CI	[redacted]	-
p-value	[redacted]	-
V5: day 43, 16:00 hours		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min	[redacted]	[redacted]
Max	[redacted]	[redacted]

	Netarsudil-latanoprost QD (N=218)	Bimatoprost-timolol QD (N=212)
Difference from bimatoprost-timolol	[redacted]	-
95% 2-sided CI	[redacted]	-
p-value	[redacted]	-
V5: day 43, diurnal mean		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min	[redacted]	[redacted]
Max	[redacted]	[redacted]
Difference from bimatoprost-timolol	[redacted]	-
95% 2-sided CI	[redacted]	-
p-value	[redacted]	-
V6: day 90, 08:00 hours		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min	[redacted]	[redacted]
Max	[redacted]	[redacted]
Difference from bimatoprost-timolol	[redacted]	-
95% 2-sided CI	[redacted]	-
p-value	[redacted]	-
V6: day 90, 10:00 hours		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min	[redacted]	[redacted]
Max	[redacted]	[redacted]
Difference from bimatoprost-timolol	[redacted]	-
95% 2-sided CI	[redacted]	-
p-value	[redacted]	-
V6: day 90, 16:00 hours		

	Netarsudil-latanoprost QD (N=218)	Bimatoprost-timolol QD (N=212)
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min	[redacted]	[redacted]
Max	[redacted]	[redacted]
Difference from bimatoprost-timolol	[redacted]	-
95% 2-sided CI	[redacted]	-
p-value	[redacted]	-
V6: day 90, diurnal mean		
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min	[redacted]	[redacted]
Max	[redacted]	[redacted]
Difference from bimatoprost-timolol	[redacted]	-
95% 2-sided CI	[redacted]	-
p-value	[redacted]	-

Source: MERCURY 3 CSR[53]

Abbreviation: CI = Confidence interval; QD = Once daily; SD = Standard deviation.

Note: Baseline refers to the visit 3 data at the corresponding time point (i.e., diurnally adjusted baseline) for each time point of visits 4, 5, and 6. For visits 7, 8, and 9, baseline refers to visit 3.1 data.

Difference from bimatoprost-timolol, 2-sided CIs, and p-values are based on 2-sample t-tests comparing netarsudil-latanoprost with bimatoprost-timolol.

*p-value <0.05; **p-value <0.01; ***p-value <0.001.

B.2.6.6 Secondary efficacy endpoint: mean percent change from baseline in diurnal IOP at each post-treatment visit – ITT population

The mean percent change from baseline in diurnal IOP was similar in the netarsudil-latanoprost ([redacted]) and bimatoprost-timolol ([redacted]) groups at month 3. There was no statistically significant difference observed (p=[redacted] [95% CI: [redacted], [redacted]]).

Equivalent results were also observed in the earlier time points. At week 2, the mean percentage change from baseline in IOP was [redacted] and [redacted], in the netarsudil-latanoprost and bimatoprost-timolol arm, respectively, with no statistically significant difference observed between the arms (p=[redacted] [95% CI: [redacted], [redacted]]). Data collected at week 6 reported similar conclusions ([redacted] and [redacted]), with no statistically significant difference (p=[redacted] [95% CI: [redacted], [redacted]]).

B.2.6.7 Secondary efficacy endpoint: percentage of subjects achieving pre-specified mean, mean change and percent mean change diurnal IOP levels at each post-treatment time point – ITT population

Using Fisher's Exact tests, netarsudil-latanoprost compared to bimatoprost-timolol was not statistically different in terms of the percentage of patients with a diurnal mean IOP of ≤22, ≤21, ≤20, ≤19, ≤18, ≤17, ≤16, ≤15, ≤14 mmHg, or in IOP reduction from baseline of ≥2, ≥4, ≥6, ≥8, ≥10, ≥12 mmHg at week 2, week 6, or month 3. The same is true for the percentage of patients with an IOP precent reduction from baseline of ≥5, ≥30, ≥35, ≥40.

B.2.6.8 Safety endpoint: change in Short Form Health Survey Questionnaire 36 score

The change in self-administered Short Form Health Survey Questionnaire 36 (SF-36) score in MERCURY 3 from baseline to study exit is presented in Table 13. Statistically significant differences between groups were reported in two subscales, "General Health" and "Mental Health" (both at the month 6 visit).

The mean SF-36 scores were comparable between the netarsudil-latanoprost and bimatoprost-timolol groups; there was no statistically significant difference between subjects treated with netarsudil-latanoprost compared to bimatoprost-timolol in the majority of subscales, suggesting that subjects randomised to either group had similar perceptions of their general health at both time points.[53] There was also no statistically significant difference within treatment groups for the mean change from baseline to month 6.[53]

Table 13: The 36-item health survey questionnaire (SF-36) – physical/mental component summary and dimension scores, by treatment group (safety population)

	Netarsudil-latanoprost QD (N=218)		Bimatoprost-timolol QD (N=212)	
	Actual	**Change from baseline**	**Actual**	**Change from baseline**
Physical component score				
V1: Screening				
n	[redacted]	-	[redacted]	-
Mean	[redacted]	-	[redacted]	-
SD	[redacted]	-	[redacted]	-
Median	[redacted]	-	[redacted]	-
Min	[redacted]	-	[redacted]	-
Max	[redacted]	-	[redacted]	-
p-value [1]	[redacted]	-	-	-
V9: Month 6				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1] p-value [2]	[redacted]	[redacted] [redacted]	-	[redacted]
V9/ET (Month 6 Completers/Early Termination):				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]

	Netarsudil-latanoprost QD (N=218)		Bimatoprost-timolol QD (N=212)	
	Actual	**Change from baseline**	**Actual**	**Change from baseline**
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1] p-value [2]	[redacted]	[redacted] [redacted]	-	[redacted]
Mental component score				
V1: Screening				
n	[redacted]	-	[redacted]	-
Mean	[redacted]	-	[redacted]	-
SD	[redacted]	-	[redacted]	-
Median	[redacted]	-	[redacted]	-
Min	[redacted]	-	[redacted]	-
Max	[redacted]	-	[redacted]	-
p-value [1]	[redacted]	-	-	-
V9: Month 6				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1]	[redacted]	[redacted]	-	[redacted]

	Netarsudil-latanoprost QD (N=218)		Bimatoprost-timolol QD (N=212)	
	Actual	**Change from baseline**	**Actual**	**Change from baseline**
p-value [2]		[redacted]		
V9/ET (Month 6 Completers/Early Termination):				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1] p-value [2]	[redacted]	[redacted]	-	[redacted]
Physical functioning				
V1: Screening				
n	[redacted]	-	[redacted]	-
Mean	[redacted]	-	[redacted]	-
SD	[redacted]	-	[redacted]	-
Median	[redacted]	-	[redacted]	-
Min	[redacted]	-	[redacted]	-
Max	[redacted]	-	[redacted]	-
p-value [1]	[redacted]	-	-	-
V9: Month 6				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]

	Netarsudil-latanoprost QD (N=218)		Bimatoprost-timolol QD (N=212)	
	Actual	**Change from baseline**	**Actual**	**Change from baseline**
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1] p-value [2]	[redacted]	[redacted]	-	[redacted]
V9/ET (Month 6 Completers/Early Termination):				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1] p-value [2]	[redacted]	[redacted]	-	[redacted]
Role Physical				
V1: Screening				
n	[redacted]	-	[redacted]	-
Mean	[redacted]	-	[redacted]	-
SD	[redacted]	-	[redacted]	-
Median	[redacted]	-	[redacted]	-
Min	[redacted]	-	[redacted]	-
Max	[redacted]	-	[redacted]	-
p-value [1]	[redacted]	-	-	-

	Netarsudil-latanoprost QD (N=218)		Bimatoprost-timolol QD (N=212)	
	Actual	**Change from baseline**	**Actual**	**Change from baseline**
V9: Month 6				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1] p-value [2]	[redacted]	[redacted] [redacted]	-	[redacted]
V9/ET (Month 6 Completers/Early Termination):				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1] p-value [2]	[redacted]	[redacted] [redacted]	-	[redacted]
Bodily pain				
V1: Screening				
n	[redacted]	-	[redacted]	-
Mean	[redacted]	-	[redacted]	-
SD	[redacted]	-	[redacted]	-

	Netarsudil-latanoprost QD (N=218)		Bimatoprost-timolol QD (N=212)	
	Actual	**Change from baseline**	**Actual**	**Change from baseline**
Median	[redacted]	-	[redacted]	-
Min	[redacted]	-	[redacted]	-
Max	[redacted]	-	[redacted]	-
p-value [1]	[redacted]	-	-	-
V9: Month 6				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1] p-value [2]	[redacted]	[redacted]	-	[redacted]
V9/ET (Month 6 Completers/Early Termination):				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1] p-value [2]	[redacted]	[redacted]	-	[redacted]
General health				

	Netarsudil-latanoprost QD (N=218)		Bimatoprost-timolol QD (N=212)	
	Actual	**Change from baseline**	**Actual**	**Change from baseline**
V1: Screening				
n	[redacted]	-	[redacted]	-
Mean	[redacted]	-	[redacted]	-
SD	[redacted]	-	[redacted]	-
Median	[redacted]	-	[redacted]	-
Min	[redacted]	-	[redacted]	-
Max	[redacted]	-	[redacted]	-
p-value [1]	[redacted]	-	-	-
V9: Month 6				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1] p-value [2]	[redacted]	[redacted]	-	[redacted]
V9/ET (Month 6 Completers/Early Termination):				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]

	Netarsudil-latanoprost QD (N=218)		Bimatoprost-timolol QD (N=212)	
	Actual	**Change from baseline**	**Actual**	**Change from baseline**
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1] p-value [2]	[redacted]	[redacted] [redacted]	-	[redacted]
Vitality				
V1: Screening				
n	[redacted]	-	[redacted]	-
Mean	[redacted]	-	[redacted]	-
SD	[redacted]	-	[redacted]	-
Median	[redacted]	-	[redacted]	-
Min	[redacted]	-	[redacted]	-
Max	[redacted]	-	[redacted]	-
p-value [1]	[redacted]	-	-	-
V9: Month 6				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1] p-value [2]	[redacted]	[redacted] [redacted]	-	[redacted]
V9/ET (Month 6 Completers/Early Termination):				
n	[redacted]	[redacted]	[redacted]	[redacted]

	Netarsudil-latanoprost QD (N=218)		Bimatoprost-timolol QD (N=212)	
	Actual	**Change from baseline**	**Actual**	**Change from baseline**
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1] p-value [2]	[redacted]	[redacted]	-	[redacted]
Social Functioning				
V1: Screening				
n	[redacted]	-	[redacted]	-
Mean	[redacted]	-	[redacted]	-
SD	[redacted]	-	[redacted]	-
Median	[redacted]	-	[redacted]	-
Min	[redacted]	-	[redacted]	-
Max	[redacted]	-	[redacted]	-
p-value [1]	[redacted]	-	-	-
V9: Month 6				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]

	Netarsudil-latanoprost QD (N=218)		Bimatoprost-timolol QD (N=212)	
	Actual	**Change from baseline**	**Actual**	**Change from baseline**
p-value [1] p-value [2]	[redacted]	[redacted]	-	[redacted]
V9/ET (Month 6 Completers/Early Termination):				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1] p-value [2]	[redacted]	[redacted]	-	[redacted]
Role Emotional				
V1: Screening				
n	[redacted]	-	[redacted]	-
Mean	[redacted]	-	[redacted]	-
SD	[redacted]	-	[redacted]	-
Median	[redacted]	-	[redacted]	-
Min	[redacted]	-	[redacted]	-
Max	[redacted]	-	[redacted]	-
p-value [1]	[redacted]	-	-	-
V9: Month 6				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]

	Netarsudil-latanoprost QD (N=218)		Bimatoprost-timolol QD (N=212)	
	Actual	**Change from baseline**	**Actual**	**Change from baseline**
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1] p-value [2]	[redacted]	[redacted]	-	[redacted]
V9/ET (Month 6 Completers/Early Termination):				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1] p-value [2]	[redacted]	[redacted]	-	[redacted]
Mental Health				
V1: Screening				
n	[redacted]	-	[redacted]	-
Mean	[redacted]	-	[redacted]	-
SD	[redacted]	-	[redacted]	-
Median	[redacted]	-	[redacted]	-
Min	[redacted]	-	[redacted]	-
Max	[redacted]	-	[redacted]	-

	Netarsudil-latanoprost QD (N=218)		Bimatoprost-timolol QD (N=212)	
	Actual	**Change from baseline**	**Actual**	**Change from baseline**
p-value [1]	[redacted]	-	-	-
V9: Month 6				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1] p-value [2]	[redacted]	[redacted]	-	[redacted]
V9/ET (Month 6 Completers/Early Termination):				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]
p-value [1] p-value [2]	[redacted]	[redacted]	-	[redacted]

Source: MERCURY 3 CSR[53]

Abbreviation: ET – Early termination; Max – Maximum; Min – Minimum; QD – Once daily; SD – Standard deviation;

Note: Change from baseline was defined as Visit Value - Screening Value. A higher score indicates a better perception of health.

[1] p-values, expressed as p1/p2, are based on 2-sample t-tests (p1) and Wilcoxon rank sum tests (p2) comparing netarsudil-latanoprost with bimatoprost-timolol.

[2] p-values, expressed as p1/p2, are based on paired t-tests (p1) and Wilcoxon signed-rank tests (p2) comparing differences between visit and baseline values within treatment groups.

B.2.7 Subgroup analysis

The ITT population was used for subgroup analyses and used observed data only. All subgroup analyses were pre-planned, and based on pre-study characteristics:

- Age:
  - <65 years
  - ≥65 years
- Gender:
  - Male
  - Female
- Race:
  - Caucasian
  - Other
- Iris colour:
  - Blue/grey/green
  - Brown/black
  - Hazel
- Maximum baseline IOP value:
  - <22 mmHg
  - <23 mmHg
  - <24 mmHg
  - <25 mmHg
  - <26 mmHg
  - <27 mmHg
  - <30 mmHg
  - <32 mmHg
- Prior hypotensive medication experience category 1:
  - Combination therapy
  - Prostaglandin (monotherapy)
  - Other (monotherapy)
  - No prior therapy
- Prior hypotensive medication experience category 2 (includes both monotherapies and combinations):
  - Prior prostaglandin
  - No prior prostaglandin
- Country:
  - Austria
  - Belgium
  - Czech Republic
  - France
  - Germany

- Hungary
- Italy
- Latvia
- Poland
- Spain
- UK

For each subgroup, except those defined by unmedicated baseline IOP, IOP was compared at each post-dose time point between treatment groups using an ANCOVA model with treatment as the main effect, baseline IOP and subgroup as covariates, and the interaction of treatment by subgroup. The least squares mean differences (netarsudil-latanoprost – bimatoprost-timolol) was presented as well as 2-sided 95% CIs and p-values.

A summary of the results for the subgroup analyses is presented in Appendix E.

B.2.8 Meta-analysis

A meta-analysis was not conducted, as the only relevant clinical trial identified for netarsudil-latanoprost from the SLR that is relevant to this submission is MERCURY 3.

B.2.9 Indirect and mixed treatment comparisons

As no head-to-head studies for netarsudil-latanoprost and FDCs (except for MERCURY 3) were available, an indirect treatment comparison (ITC) was required. This section presents the ITC for netarsudil-latanoprost versus the following FDCs: brimonidine-timolol, dorzolamide-timolol and brinzolamide-brimonidine.

B.2.9.1 Overview of indirect treatment comparisons considered

B.2.9.1.1 Comparative effectiveness data sources

As previously outlined in section B.1.1, it is expected that the NICE-recommended population will reflect the license wording for netarsudil-latanoprost; limited to adult patients with POAG or OHT for whom monotherapy (with a prostaglandin or netarsudil) provides insufficient IOP reduction.[60] Hence, the comparators considered for the ITC were limited to the expected comparators within this population (FDC therapies).[60]

As described in Appendix D, the SLR identified one head-to-head study comparing netarsudil-latanoprost to a FDC; the MERCURY 3 trial compared netarsudil-latanoprost to bimatoprost-timolol.[53] The SLR identified three further relevant studies that included a FDC as an intervention or comparator.[61–63] The four relevant studies identified in the SLR, that were considered for inclusion in the ITC, are summarised in Table 14.

Table 14: Relevant studies identified from the clinical SLR that included netarsudil-latanoprost or a FDC

Trial name	Intervention(s)	Study design	Primary endpoint
MERCURY 3[53]	Arm 1: Netarsudil-latanoprost (n=218) Arm 2: Bimatoprost-timolol (n=212)	Prospective, double-blinded, randomised, multicentre, active-controlled, parallel-group, phase III trial. Based across 11 countries.	Mean IOP at specified time points at week 2, week 6 and month 3

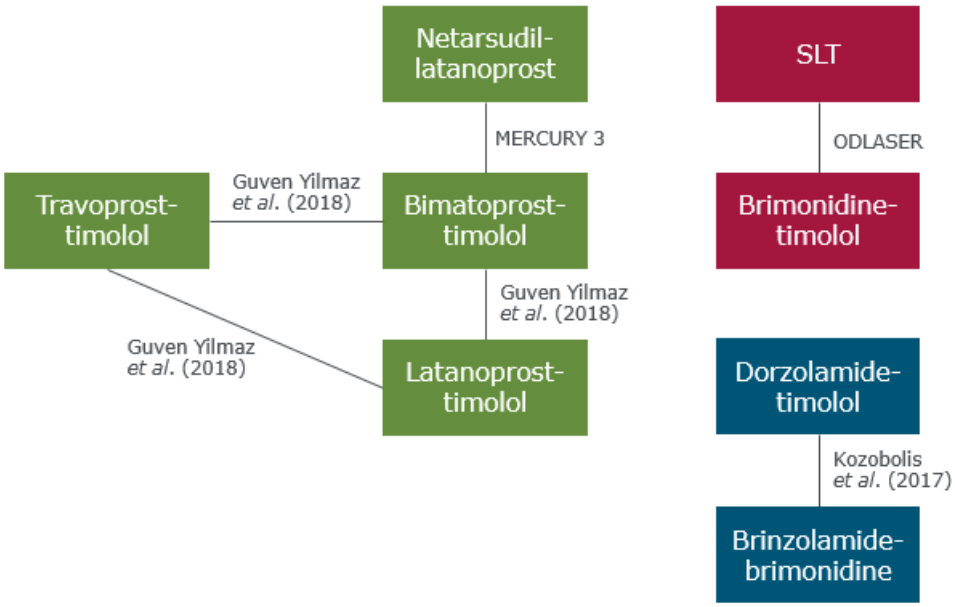
ODLASER[61]	Arm 1: SLT (n=12) Arm 2: Brimonidine-timolol (n=11)	Prospective, single-blinded (investigator), randomised, pilot study. Based in the USA.	Reduction in IOP from baseline at 8 weeks
Kozobolis *et al*. (2017)[62]	Arm 1: Brinzolamide-brimonidine (n=22) Arm 2: Dorzolamide-timolol (n=22)	Prospective, randomised, double-blinded, parallel-group. Based in Greece.	IOP at specified time points (morning and afternoon) at week 1, week 4, week 8 and week 12
Guven Yilmaz *et al*. (2018)[63]	Arm 1: Brimonidine-timolol maleate (n=18) Arm 2: Latanoprost-timolol maleate (n=14) Arm 3: Travoprost-timolol maleate (n=18)	Prospective, observer-masked, randomised study. Based in Turkey.	IOP at specified time points (10:00, 14:00, 18:00, 22:00, 02:00) over 24 hours

Abbreviations: FDC – Fixed-dose combination; IOP – Intraocular pressure; SLR – Systematic literature review; SLT – Selective laser trabeculoplasty; USA – United States of America

B.2.9.1.2 Choice of ITC

The network of evidence for netarsudil-latanoprost and FDCs based on the four relevant RCTs identified in the SLR is presented in Figure 8.

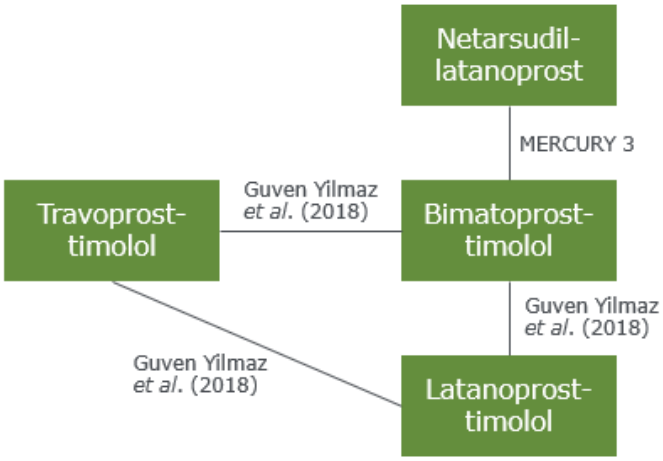
Figure 8: Evidence network



Abbreviations: SLT – Selective laser trabeculoplasty

Since two of the studies, MERCURY 3 and Guven Yilmaz *et al*. (2018), formed a connected network, the feasibility of a network meta-analysis (NMA) based on these two studies was considered first. The connected evidence network, for which the feasibility of a NMA was assessed, is shown in Figure 9.

Figure 9: Connected evidence network



B.2.9.1.2.1 NMA feasibility assessment overview

Outcomes of interest

The feasibility of a NMA was assessed using aggregate data from the MERCURY 3 and Guven Yilmaz *et al.* (2018) studies. A summary of the endpoints considered and the justification for considering these is summarised in Table 15.

Table 15: Outcomes considered for inclusion in the NMA

Endpoints of interest in the cost-effectiveness model (CEM)	Justification
Percentage change from baseline in diurnal IOP	• Health states in the CEM are based on percentage reduction thresholds in IOP. • Using IOP as the efficacy outcome in the CEM aligns with the measure used for the primary endpoint in MERCURY 3. • NICE identifies IOP as a useful and conveniently measured 'surrogate outcome' for treatment success in glaucoma, with the aim of OAG treatment being to lower IOP, thus preserving visual function.[64] • Diurnal IOP provides a more holistic picture of patient progress, accounting for daily fluctuations. • Percentage change in IOP accounts for the range of initial baseline levels from patients in the trials. This is particularly important as the ITC pools data from different trials where baseline characteristics and eligibility criteria were not identical. • Long-term lowering of IOP remains the only strategy known to be effective against conversion to chronic OAG and sight loss, and control of IOP remains critical to current therapeutic approaches.[64] • It has been shown that greater IOP reduction is associated with a greater reduction in disease progression, as defined by the rate of visual field progression in patients with primary OAG. As such, patients with a larger reduction from baseline in IOP are likely to experience higher quality-of-life and lower costs compared to those with a smaller reduction.[64,65]

DDTAE	To enable comparisons of interventions in the CEM according to their safety and discontinuation profiles.
Incidence of TEAEs	

Abbreviations: CEM – Cost-effectiveness model; DDTAE – Discontinuation due to adverse events; IOP – Intraocular pressure; NMA – Network meta-analysis; TEAE – Treatment-emergent adverse event

IOP

An overview of IOP data from the two trials considered in the NMA feasibility assessment is presented in Table 16. The study length of the Guven Yilmaz *et al*. (2018) trial was one day only, which was considered unsuitable for direct comparison with data from MERCURY 3, where six months of data were recorded. This invalidated the comparison between Guven Yilmaz *et al*. (2018): therefore, an NMA for the IOP outcome was concluded as infeasible.[63]

Other outcomes considered included the use of time point (non-diurnal) outcomes, the use of actual reduction (non-percentage), and a combination of both alternatives. The reasons for the use of 'percentage reduction from baseline in diurnal IOP' are outlined in Table 15.

Table 16: Method of IOP assessment and data availability

Study	Outcome definition	Time point	Sufficient data
MERCURY 3[53]	• Actual mean IOP (08:00, 10:00, 16:00) • Actual change from baseline (08:00, 10:00, 16:00) • Least squares change in actual IOP (08:00, 10:00, 16:00) • Mean diurnal (average hourly values: 08:00, 10:00, 16:00)	6 months (180 days) • Week 2, Week 6, week 12	Yes – sufficient data available to calculate aggregate percentage change from baseline in IOP.
Guven Yilmaz *et al*. (2018)[63]	• Mean IOP (08:00, 14:00, 18:00, 22:00, 02:00) • Mean diurnal variation in IOP (08:00, 14:00, 18:00, 22:00, 02:00) • Mean nocturnal variation in IOP (08:00, 14:00, 18:00, 22:00, 02:00)	24 hours (1 day)	No – time point of 24 hours is too short and not comparable to MERCURY 3.

Abbreviations: IOP – Intraocular pressure; NR – Not reported

Discontinuation due to adverse events (DDTAE)

An overview of DDTAE from the two trials considered in the NMA feasibility assessment is presented in Table 17. Guven Yilmaz *et al*. (2018) did not report DDTAE.[63] Therefore, it was not feasible to conduct an NMA using DDTAE as an outcome.

Table 17: Method of DDTAE assessment and data availability

Study	Outcome definition	Time point	Sufficient data
MERCURY 3[53]	Number and percentage of subjects with AEs resulting in study treatment discontinuation, by treatment group	6 months (180 days)	Yes – sufficient data available.
Guven Yilmaz *et al*. (2018)[63]	NR	24 hours (1 day)	No – data for DDTAE NR.

Abbreviations: DDTAE – Discontinuation due to adverse events; NR – Not reported

TEAEs

An overview of TEAEs from the two trials considered in the NMA feasibility assessment is presented in Table 18. Guven Yilmaz *et al*. (2018) did not report TEAEs.[63] Therefore, it was not feasible to conduct an NMA using TEAEs as an outcome.

Table 18: Method of TEAE assessment and data availability

Study	Outcome definition	Time point	Sufficient data
MERCURY 3[53]	• Overall summary of TEAEs by treatment group • Ocular TEAEs occurring at an incidence of ≥1% • Severity of ocular TEAEs occurring at an incidence of ≥5% • Ocular TEAEs occurring in ≥1% of subjects in any treatment group • SAEs	6 months (180 days)	Yes – sufficient data available.
Guven Yilmaz *et al*. (2018)[63]	NR	24 hours (1 day)	No – data for TEAEs NR.

Abbreviations: NR – Not reported; SAE – Serious adverse event; TEAE – Treatment-emergent adverse event

Conclusion

It was determined that an NMA based on the connected network (Figure 9) containing netarsudil-latanoprost, bimatoprost-timolol, travoprost-timolol and latanoprost-timolol was infeasible due to unavailable or insufficient data in the Guven Yilmaz *et al*. (2018) study; data was unavailable or insufficient for all outcomes of interest (IOP, DDTAE and TEAEs). As such, the Guven Yilmaz *et al*. (2018) study was excluded and hence, the feasibility assessment of an unanchored ITC (an ITC without a common comparator) was considered, described in the next section.

B.2.9.1.2.2 MAIC and STC overview

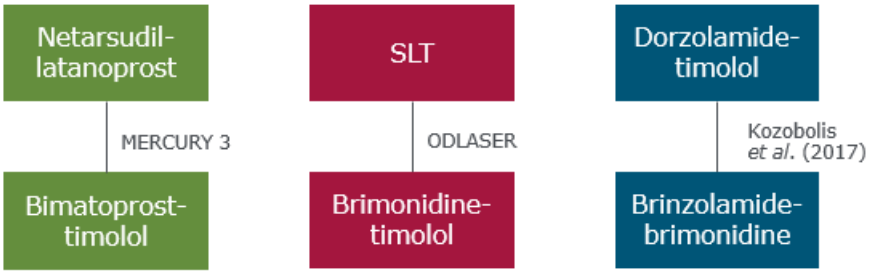
As an NMA was deemed infeasible, unanchored methods were the only other option for comparison. Therefore, the methods considered to inform the comparative efficacy data for netarsudil-latanoprost versus FDCs in the cost-effectiveness model were an unanchored matching-adjusted indirect comparison (MAIC), naïve comparison, and simulated treatment

comparison (STC), in line with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18.[66]

MAIC and STC modelling were deemed appropriate to explore given that they have less restrictive data requirements compared to other ITC methods. MAIC and STCs require individual patient-level data (IPD) to be available for at least one of the treatments included in the comparison, with aggregate data being sufficient for all other treatments. This is the case in this submission, where IPD are available from the MERCURY 3 trial and aggregate data are available from the ODLASER and Kozobolis *et al.* (2017) trials. Furthermore, in unanchored MAIC and STC analyses, a common comparator does not need to be present within the evidence base, which was the case across the network.

The evidence network considered for the unanchored ITC is displayed in Figure 10, showing an unanchored evidence network containing the following studies: MERCURY 3, ODLASER and Kozobolis *et al*. (2017).[53,61,62] The Guven Yilmaz *et al*. (2018) study was previously excluded from this network on the basis of insufficient reporting of the outcomes of interest, namely IOP, DDTAE and TEAEs, as described in section B.2.9.1.2.1.[63]

Figure 10: Unanchored ITC evidence network



Abbreviations: SLT – Selective laser trabeculoplasty

An unanchored MAIC and STC were explored to control for population characteristics whilst accounting for the data unavailability and lack of links in the network. This followed the NICE TSD 18 recommendation of an ITC (unanchored MAIC or STC) in the absence of a connected network of randomised studies, or where there are single-arm studies involved.[66] Furthermore, the use of an unanchored MAIC and STC was accepted by the NICE committee in a recent appraisal, and the evidence review group (ERG) noted that both methods could be used to adjust for between-study differences in baseline patient characteristics in the absence of randomisation.[66,67] There is precedent for the use of a MAIC; the approach was endorsed by the ERG in ocular HTAs submitted to and accepted by NICE, most recently, the evaluation of dexamethasone intravitreal implant (TA824) for the treatment of diabetic macular oedema, for which a MAIC was conducted.[67]

The MAIC, STC and naïve analyses considered are outlined below:

- Unanchored MAIC, controlling for two covariates, for IOP percentage reduction from baseline of netarsudil 0.02%/latanoprost 0.005% versus
    - Brimonidine 0.2%/timolol maleate 0.5% FDC
    - Dorzolamide 2%/timolol 0.5% FDC
    - Brinzolamide/brimonidine FDC
- STC of netarsudil 0.02%/latanoprost 0.005% versus

    - Brimonidine 0.2%/timolol maleate 0.5% FDC
    - Dorzolamide 2%/timolol 0.5% FDC
    - Brinzolamide/brimonidine FDC
- Naïve comparison of netarsudil 0.02%/latanoprost 0.005% versus
    - Brimonidine 0.2%/timolol maleate 0.5% FDC
    - Dorzolamide 2%/timolol 0.5% FDC
    - Brinzolamide/brimonidine FDC

The feasibility assessment and methodology for the unanchored MAIC and STC are presented in Appendix D and summarised in section B.2.9.2 and B.2.9.3.

B.2.9.1.3 Comparison of patients' baseline characteristics between the MERCURY 3, ODLASER and Kozobolis *et al*. (2017) clinical trials

Table 19 summarises the baseline characteristics of the three RCTs considered in the ITC feasibility assessment. Several differences in patients' characteristics were noted across the MERCURY 3, ODLASER and Kozobolis *et al*. (2017) trials.

MERCURY 3 and Kozobolis *et al*. (2017) were aligned on inclusion/exclusion criteria surrounding age, with patients aged 18 years or older eligible for study participation.[53,62] ODLASER however differed, as only patients who were between 25-90 years old were eligible for inclusion.[61] Nonetheless, across the three trials and all treatment arms, the mean baseline age varied minimally between 65.2 years and 67.3 years.[53,61,62]

Only MERCURY 3 explicitly reported the study eye diagnosis of patients, and included both OAG or OHT patients in the trial.[53(p3)] ODLASER and Kozobolis *et al.* (2017) only included patients with POAG reflecting the eligibility criteria for both studies.

Mean IOP at baseline ranged from 24.8 - 25.1 mmHg in the MERCURY 3 trial.[53] This was slightly higher in the Kozobolis *et al.* (2017) study, ranging from 28.0 - 28.2 mmHg, and slightly lower in the ODLASER study (20.8 - 21.3 mmHg).[61,62]

Only MERCURY 3 reported the visual field mean deviation, corneal thickness, and cup to disc ratio of patients at baseline. The corneal thickness and cup to disc ratio were comparable between the treatment arms of MERCURY 3, whilst visual field mean deviation had greater variation between treatment arms at [redacted] dB for the netarsudil-latanoprost arm, and [redacted] dB for the bimatoprost-timolol arm.[53]

Previous treatments were broadly similar between MERCURY 3 and ODLASER; all patients had received previous treatment with PGAs, combinations, or other monotherapies, though there was some variation in the proportion of PGA-only treated patients. In contrast, Kozobolis *et al*. (2017) included treatment naïve patients; 45.5% and 40.9% of patients were treatment naïve in the dorzolamide-timolol and brinzolamide-brimonidine treatment arms, respectively.[62] However, since previous treatment was not validated as a key effect modifier or prognostic variable by a UK clinical expert,[68] the difference in previous treatments between trials was not expected to cause bias in the ITC results.

The differences between populations in MERCURY 3, ODLASER and Kozobolis *et al.* (2017) trials supported the need for a population-adjusted indirect comparison method, to allow a

more accurate estimate of the relative efficacy of netarsudil-latanoprost to the available FDCs in more closely aligned populations.

Table 19: Comparison of baseline characteristics in the studies considered for the ITC

Baseline characteristics	Availability in netarsudil-latanoprost trial		Availability in comparator trials			
	MERCURY 3[53]		**ODLASER**[61]		**Kozobolis *et al*. (2017)**[62]	
	Netarsudil 0.02%/latanoprost 0.005%	**Bimatoprost 0.03%/timolol 0.5%**	**SLT**	**Brimonidine tartrate 0.2%/timolol maleate 0.5%**	**Dorzolamide 2%/timolol 0.5%**	**Brinzolamide/brimonidine**
Age (years), mean ± SD	67.3 ± 12.03	67.0 ± 11.27	66.1 ± 10.4	65.9 ± 9.2	65.2 ± 7.9	65.3 ± 6.5
IOP at screening – study eye (mmHg), mean ± SD	[redacted]	[redacted]	NR	NR	NR	NR
Mean diurnal IOP (mmHg) at baseline, mean ± SD	Day 1: 25.054 ± 3.4051 Week 2: 15.39 ± [redacted]	Day 1: 24.814 ± 3.2555 Week 2: 15.56 ± [redacted]	21.3 ± 3.9	20.8 ± 4.7	Morning: 28.0 ± 2.4 Afternoon: 28.2 ± 2.5	Morning: 28.0 ± 2.4 Afternoon: 28.2 ± 2.5
Visual field mean deviation (dB), mean ± SD	[redacted]	[redacted]	NR	NR	NR	NR
Corneal thickness (µm), mean ± SD	[redacted]	[redacted]	NR	NR	NR	NR
Family history of glaucoma	NR	NR	NR	NR	NR	NR
Cup to disc ratio, mean ± SD	[redacted]	[redacted]	NR	NR	NR	NR
Disc haemorrhages	NR	NR	NR	NR	NR	NR
Baseline visual field indices	NR	NR	NR	NR	NR	NR
Retinal nerve fibre layer	NR	NR	NR	NR	NR	NR

Baseline characteristics	Availability in netarsudil-latanoprost trial		Availability in comparator trials			
	MERCURY 3[53]		**ODLASER**[61]		**Kozobolis *et al*. (2017)**[62]	
	Netarsudil 0.02%/latanoprost 0.005%	**Bimatoprost 0.03%/timolol 0.5%**	**SLT**	**Brimonidine tartrate 0.2%/timolol maleate 0.5%**	**Dorzolamide 2%/timolol 0.5%**	**Brinzolamide/brimonidine**
Corneal hysteresis	NR	NR	NR	NR	NR	NR
Previous treatment[a]	Prior combination, PGA, or other monotherapies: 100% Prior PGA therapy Yes: 78.4% No: 21.6%	Prior combination, PGA, or other monotherapies: 100% Prior PGA therapy Yes: 69.3% No: 30.7%	Prior PGA therapy: 100% Latanoprost: 33.3% Bimatoprost: 41.7% Travoprost: 25.0%	Prior PGA therapy Any PGA: 100% Latanoprost: 18.2% Bimatoprost: 72.7% Travoprost: 9.1%	Other medications Naïve: 45.5% Washout: 54.5%	Other medications Naïve: 40.9% Washout: 59.1%

Abbreviations: dB – Decibels; IOP – Intraocular pressure; ITC – Indirect treatment comparison; mmHg – Millimetres of mercury; NR – Not reported; SD – Standard deviation; SLT – Selective laser trabeculoplasty; µm – Micrometres

[a]Previous treatment was not deemed to be a key prognostic variable or treatment effect modifier for the MAIC; previous treatment is included in baseline characteristics comparison to assess the implications of varying study eligibility criteria between the network.

B.2.9.2 Unanchored MAIC

B.2.9.2.1 Outcomes

Based on the results of the feasibility assessment, as described in section B.2.9.1, it was determined that analyses via an unanchored MAIC was feasible for 'percentage reduction from baseline in diurnal IOP'.

B.2.9.2.2 Methodology

The MAIC methodology used followed the guidance produced by NICE DSU in the Technical Support Document (TSD) 18.[66]

MAIC models generate estimates for comparative effectiveness by reweighting IPD from one source to match the population of another, based on its aggregate baseline characteristics data. By generating this adjusted dataset, MAICs aim to eliminate any bias due to differences in the baseline characteristics of patients, such that the differences across the datasets are driven by treatment effect alone.

Predicting outcome and assessing treatment effects

The IOP outcomes on netarsudil-latanoprost for individuals comparable to the ODLASER and Kozobolis *et al*. (2017) populations were estimated by reweighting the outcomes observed in the MERCURY 3 trial. NICE TSD 18 recommends that treatment effects should be estimated on the linear predictor scale, with the same link functions that are usually employed for the outcome.[66] For mean IOP therefore, treatment effects were estimated by weighted absolute mean difference from the linear regression model with standard errors calculated using a robust sandwich estimator. These were presented alongside naïve unweighted estimates.

Statistical model summary

Statistical modelling was based on IPD from the ITT population of MERCURY 3 and aggregate data from the ODLASER and Kozobolis *et al*. (2017) clinical trials, separately. The analysis followed the below steps (described in further detail later in this section):

- Create a logistic propensity score model (using IPD from MERCURY 3) including effect modifiers and prognostic variables; age at baseline and IOP at baseline.

- Estimate the weights to match covariate distributions in MERCURY 3 for netarsudil-latanoprost to brimonidine-timolol, dorzolamide-timolol, and brinzolamide-brimonidine individually from the ODLASER and Kozobolis *et al*. (2017) populations using the method of moments.

- Predict outcomes for brimonidine-timolol, dorzolamide-timolol, and brinzolamide-brimonidine versus netarsudil-latanoprost in the ODLASER and Kozobolis *et al*. (2017) populations, separately, by reweighting individuals in MERCURY 3 to match those in each population.

- Perform indirect comparisons in the population of ODLASER and Kozobolis *et al*. (2017), calculating standard errors using a robust estimator. One measure of treatment effect was considered: Absolute mean difference.

Model assessment and reporting

The suitability of the propensity score model was first assessed by checking the distribution of the covariates adjusted for in the MAIC (age and baseline IOP), in the weighted intervention

MERCURY 3 pseudo-population compared with the target ODLASER and Kozobolis *et al*. (2017) population.

The distribution of weights was assessed for the presence of extreme or highly variable weights, which could cause unstable estimates. Finally, the suitability of the model was assessed through the evaluation of the ESS of the weighted pseudo-population; a large reduction in ESS may indicate poor overlap between the MERCURY 3 and ODLASER or Kozobolis *et al*. (2017) populations, and the resulting comparison may be unstable.

Programming language for the indirect or mixed treatment comparison

The MAIC analyses was conducted in the freely available software package R, using code modified from the NICE TSD18, which uses the following R packages: dplyr, tidyr, readr, readxl, ggplot2, sandwich, janitor, hmisc, diagis, survey, finalfit.[66]

Summary of analyses

An unanchored MAIC was used to assess the comparative effectiveness of netarsudil-latanoprost vs. brimonidine-timolol, dorzolamide-timolol, and brinzolamide-brimonidine. The following outputs were assessed:

- Weighted absolute mean difference from the linear regression model with standard errors calculated using a robust sandwich estimator.

B.2.9.2.3 Covariate selection

To determine the list of factors included in the population adjustment, a UK clinical expert was presented with a list of potential prognostic variables and treatment effect modifiers, that may affect the prognosis or treatment outcomes in patients with POAG or OHT. The list of factors was retrieved from targeted literature searches, and is presented in Table 20.

Table 20: Potential treatment effect modifiers and prognostic variables

	Supported in the published literature[a]										
	Ernest *et al.* (2014)[69]	**Lee *et al.* (2014)[70]**	**European Glaucoma Prevention Study (2007)[71]**	**Hayakawa *et al.* (1994)[72]**	**Leske *et al.* (2003)[73]**	**Collaborative normal-tension glaucoma study[74]**	**Allison *et al.* (2020)[52]**	**Gazzard *et al.* (2019)[75]**	**Gordon *et al.* (1999)[76]**	**Kass *et al.* (2002)[40]**	**Chrisholm *et al.* (1989)[77]**
Age	✓	✓	✓	✗	✓	✗	✗	✗	✓	✓	✓
IOP	✓	✗	✗	✓	✓	✗	✗	✓	✓	✓	✗
Family history of glaucoma	✗	✗	✗	✗	✗	✓	✗	✓	✓	✗	✗
Baseline visual field loss/indices	✓	✗	✗	✓	✗	✗	✗	✗	✓	✓	✗
Visual field mean deviation	✗	✓	✗	✓	✓	✗	✗	✓	✗	✓	✓
Disc haemorrhages	✓	✗	✗	✗	✓	✓	✗	✗	✗	✗	✗
(Vertical) cup to disc ratio	✗	✓	✓	✗	✗	✗	✗	✗	✓	✓	✗
Central (and lower central) corneal thickness	✗	✗	✓	✗	✗	✗	✗	✓	✗	✓	✗

Abbreviations: IOP – Intraocular pressure

[a] Only the factors listed in three or more publications are shown in the table.

The clinical expert was asked to do the following:

- Categorise the prognostic variables and treatment effect modifiers considered critical to include in the MAIC, or good to include if the data allows
- Following categorisation, rank the prognostic variables and treatment effect modifiers from most to least important for inclusion in the MAIC

Table 21 displays the results of the validation, grouping the variables into those considered critical or beneficial for inclusion within the MAIC. A third category was also used for variables that were not deemed key prognostic variables or treatment effect modifiers for the MAIC, though it was noted substantial imbalances may impact the robustness of any analyses.

Table 21: Prognostic variables and treatment effect modifiers validation

Potential prognostic variables and TEMs	Critical for inclusion	Beneficial for inclusion	Available in MERCURY 3	Available in ODLASER and Kozobolis *et al*. (2017)	Included in ITC models
Age (baseline/screening)	[redacted]	[redacted]	[redacted]	✓	✓ Base-case analysis
IOP (baseline/screening)	[redacted]	[redacted]	[redacted]	✓	✓ Base-case analysis
Visual field mean deviation	[redacted]	[redacted]	[redacted]	✗	✗
Corneal thickness	[redacted]	[redacted]	[redacted]	✗	✗
Family history of glaucoma	[redacted]	[redacted]	[redacted]	✗	✗
Cup to disc ratio	[redacted]	[redacted]	[redacted]	✗	✗
Disc haemorrhages	[redacted]	[redacted]	[redacted]	✗	✗
Baseline visual field indices	[redacted]	[redacted]	[redacted]	✗	✗
RNFL	[redacted]	[redacted]	[redacted]	✗	✗
Corneal hysteresis	[redacted]	[redacted]	[redacted]	✗	✗
Study eye diagnosis (POAG or OHT)	[redacted]	[redacted]	[redacted]	✓	✓ Sensitivity analysis[e]
Previous treatment[d]	[redacted]	[redacted]	[redacted]	✓	✗

Abbreviations: IOP – Intraocular pressure; N/A – Not available; OAG – Open-angle glaucoma; OHT – Ocular hypertension; POAG – Primary open-angle glaucoma; RNFL – Retinal nerve fibre layer; TEM – Treatment effect modifier

[a]MERCURY 3 reported ocular medical history of patients, not family history of glaucoma.

[b]MERCURY 3 reported visual acuity scores instead of baseline visual field indices.

[c]Study eye diagnosis was identified as neither a prognostic variable nor treatment effect modifier, but as having potential to impact the robustness of analysis if substantial differences were present. This variable was analysed as an exception due to a notable level of heterogeneity.

[d]Previous treatment was not deemed to be a key prognostic variable or treatment effect modifier for the MAIC. Previous treatment is included in comparisons between the baseline characteristics to facilitate comparisons based on study inclusion and exclusion criteria between the RCTs.

[e]The sensitivity analysis for study eye diagnosis comprised a direct restriction of the MERCURY 3 population; use of study eye diagnosis as a matching variable would not be intuitive, as no patients would constitute a match due to ODLASER and Kozobolis *et al*. (2017) only containing POAG patients.

Only two of the critical for inclusion or beneficial for inclusion factors identified by the clinical expert (age and IOP at baseline) could be included as covariates, based on the availability of data for baseline characteristics across the three trials: age [mean, years] and IOP [mean, mmHg].

B.2.9.2.4 Results

Effective sample size

Upon running the MAIC analyses, concerns arose regarding the insufficient effective sample sizes that were produced after weighting the MERCURY 3 IPD. Table 22 presents the unweighted and weighted sample size of the MERCURY 3 IPD. The unweighted sample size for the MERCURY 3 IPD (n=[redacted]) is lower than the total number of patients in the study (n=218) due to the removal of patients who did not report observations at all three time points (08:00, 10:00, 16:00) during the visits.

Table 22: Unweighted and weighted sample sizes in the MERCURY 3 IPD MAIC analyses

MAIC analysis of netarsudil-latanoprost (MERCURY 3 IPD) vs.	MERCURY 3 IPD unweighted sample size	MERCURY 3 IPD weighted sample size
Brimonidine-timolol (ODLASER)[61]	[redacted]	[redacted]
Brinzolamide-brimonidine (Kozobolis *et al*. [2017])[62]		[redacted]
Dorzolamide-timolol (Kozobolis *et al*. [2017])[62]		[redacted]

Abbreviations: IPD – Individual patient-level data; MAIC – Matching-adjusted indirect treatment comparison

Individual patient weightings

Figure 11, Figure 12 and Figure 13 show the histograms of rescaled weights for each respective population. They demonstrate that some patients have very large weights for each comparison, indicating potentially unstable estimates.

Figure 11: Histogram of rescaled MERCURY 3 weights with Kozobolis *et al*. (2017) (dorzolamide-timolol)

Abbreviations: ESS – Effective sample size

Figure 12: Histogram of rescaled MERCURY 3 weights with Kozobolis *et al*. (2017) (brinzolamide/brimonidine) target population

Abbreviations: ESS – Effective sample size

Figure 13: Histogram of rescaled MERCURY 3 weights with ODLASER target population

Abbreviations: ESS – Effective sample size

Efficacy results

Table 23 shows the unweighted and weighted MERCURY 3 IPD for the selected covariates.

Table 23: Unweighted and weighted MERCURY 3 IPD for age and baseline IOP

Target population	Unweighted IPD for age (mean, SD)	Weighted IPD for age (mean, SD)	Unweighted IPD for baseline IOP (mean, SD)	Weighted IPD for baseline IOP (mean, SD)
Kozobolis *et al*. (2017)[62] (dorzolamide-timolol)	[redacted]	[redacted]	[redacted]	[redacted]

Kozobolis *et al*. (2017)[62] (brinzolamide-brimonidine)	[redacted]	[redacted]	[redacted]	[redacted]
ODLASER[61] (brimonidine-timolol)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IOP- Intraocular pressure; IPD - Individual patient-level data; SD - Standard deviation.

For each comparator, the STC and MAIC calculated the absolute mean difference between the IOP percentage reduction of netarsudil-latanoprost and the weighted outcomes for each comparator. These were applied to the IPD which informed the transitions from the MERCURY 3 data, increasing the percentage reduction in IOP by the fixed amount for each patient and time point. This created a new set of transitions across the three IOP health states for each comparator. Transition probabilities are explained in detail, with display of the ITC applied matrices, in section B.3.3.2.

The comparator absolute mean differences produced by the MAIC are listed in Table 24. Two sets of results were produced, depending on the time point of data in each of the trials, to maximise the data input whilst managing for heterogeneity in reporting. The time points listed refer to the ODLASER, MERCURY 3, and Kozobolis *et al.* (2017) trials, respectively.

Table 24: MAIC output - Comparator absolute mean differences

Time point*	**Week 8, 12, and 12**		**Week 8, 12, and 12**	
Comparator	**Treatment effect of percentage change in IOP**	**SE of treatment effect**	**Treatment effect of percentage change in IOP**	**SE of treatment effect**
Dorzolamide-timolol	[redacted]	[redacted]	[redacted]	[redacted]
Brimonidine-timolol	NA	NA	[redacted]	[redacted]
Brinzolamide-brimonidine	[redacted]	[redacted]	[redacted]	[redacted]

Grey cells specify which data were not used in the base case; white cells maximise the evidence input whilst managing for heterogeneity in reporting.

*This row specifies from what time point, besides baseline, data from ODLASER, MERCURY 3, and Kozobolis *et al*. (2017) were taken, respectively.

Netarsudil-latanoprost data were taken from MERCURY 3; brimonidine-timolol data were taken from ODLASER; dorzolamide-timolol and brinzolamide-brimonidine data were taken from Kozobolis *et al*. (2017).

Abbreviations: IOP - Intraocular pressure; MAIC - Matching-adjusted indirect comparison; NA - Not available; SE - Standard error

B.2.9.2.5 Limitations

The MAIC represents a source of comparative effectiveness for the patient population of interest to this appraisal, aiming to adjust where feasible, for cross-study differences in patient characteristics and manage the lack of comparator data. Nonetheless, in light of the unresolvable limitations and considerable uncertainty associated with the MAIC discussed below, this analysis is considered as a scenario in this appraisal, with the STC analysis used in the base case.

Firstly, the overlap of matching covariates (age at baseline and IOP at baseline) between the comparator trial datasets and MERCURY 3 was limited, considerably impacting the sample size (from N=[redacted] in the naïve comparison to an ESS of between N=[redacted] and N=[redacted] after weighting) when the MAIC analysis was conducted. This impacts the population available for the analysis and may affect the generalisability of the cohort, and reliability of the results; however, it is difficult to predict the magnitude of impact and direction of the potential resulting bias.

Further to the matching covariates, study eye diagnosis (POAG or OHT) was a baseline characteristic available for comparison across the trials. Study eye diagnosis was comparable in the ODLASER and Kozobolis *et al.* trials, but MERCURY 3 differed by including OHT patients, reflecting a variation in inclusion criteria across the studies. Study eye diagnosis was not identified as a key effect modifier or prognostic variable, so a sensitivity analysis to remove these patients from the ITC procedures and evaluate the variation was considered sufficient to manage this difference.

Previous treatment was also evaluated, with some variation found between studies. All trials required patients to not have received eye operations or surgeries, and not have contraindications to regimens in the treatment arms (note: these are specific to the treatment arms).[53,61,62] MERCURY 3 also required patients to be 'in need for combination therapy', and not have undergone systemic medications or topical steroids.[53] This discrepancy is not likely to impact results substantially, as patients across the three trials had similar topical therapy history, and surgery criteria were equivalent, ensuring patients were at a similar stage in the treatment pathway and in disease severity.

A MAIC requires much stronger assumptions than an anchored comparison, for instance that all important prognostic and effect modifiers can be accounted for. Due to limitations in the data reported in the comparator datasets, it was not possible to adjust for all imbalances in the important prognostic factors and treatment effect modifiers identified by the UK clinical expert. Specifically, visual field mean deviation, corneal thickness, and family history of glaucoma were not reported in the comparator datasets and therefore could not be adjusted for. Other characteristics which were not considered critical, but would have improved analysis, included cup to disc haemorrhages, baseline visual field indices, retinal nerve fibre layers, and corneal hysteresis. In addition, it is not possible to compare the cohorts for those baseline characteristics and thus, it is difficult to assess how differences, if any, may impact the results.

This indicates that the results produced from such small sample sizes combined with the remaining areas of uncertainty generate plausible but unreliable estimates of the relative efficacy of netarsudil-latanoprost versus the comparators.

Based on the substantial decrease in sample size in the weighted IPD from the MAIC analyses, it was considered that MAIC may not be optimal for use in the submission modelling base case. The MAIC output is used in the model as a sensitivity analysis (see section B.3.10.3.9). There is precedent for the use of a STC; the approach has been used in ocular HTAs submitted to and accepted by NICE, most recently the evaluation of dexamethasone intravitreal implant (TA824) for the treatment of diabetic macular oedema, for which a STC was conducted.[67]

As a further sensitivity analysis, the naïve comparison is included in the model, however is subject to considerable limitations as this method does not attempt to address any of the observed differences in baseline characteristics noted in this section. A strength of the naïve comparison versus the MAIC is that it utilises all of the available data and does not reduce the ESS; however, the STC method also achieves this while attempting to adjust for differences in baseline characteristics between studies, in addition to being recommended in TSD 18 as an option for unanchored ITCs.

B.2.9.3 STC

In addition to the unanchored MAIC, an STC was also explored, as this method is also recommended as an option for adjusted ITCs in NICE TSD 18.[66]

B.2.9.3.1 Outcomes

Based on the results of the feasibility assessment, described in section B.2.9.1, it was determined that analyses via an unachored ITC were feasible for 'percentage reduction from baseline in diurnal IOP', consistent with those used in the MAIC.

B.2.9.3.2 Methodology

The methodology used in the STC followed the guidance produced by NICE TSD 18.[66]

STC models generate estimates for comparative effectiveness by using predictive equations to model the relationship between outcomes and baseline characteristics from aggregate data. The outcomes of the index treatment are then predicted in the context of the comparator population, to provide adjusted outcomes comparable to the comparator trial. By generating the adjusted outcomes, STCs facilitate comparison to multiple comparators, particularly when reweighting the population leads to an imbalanced distribution of weights or small population, from a lack of overlap in adjusted variables. The baseline characteristics in the studies were considered sufficiently comparable to run an STC.

A linear regression model looking at the relationship between the feasible effect modifiers (age and baseline IOP) and outcome of interest (percentage change in IOP) in the netarsudil-latanoprost IPD was constructed, and the resulting model used to estimate the expected outcome for the comparator trial population.

The standard error (SE) of the adjusted outcomes was estimated using the robust sandwich estimator method. The SE and mean point estimate were used to compute the confidence intervals (CIs) for all intervention outcomes, as shown in Equation 1.

Equation 1: Computation of intervention 95% CIs

$$CIs = Mean\ point\ estimate +/- 1.96\ x\ SE$$

As the comparator outcomes for percentage change in IOP were estimated from the aggregate trial data, measures of variance were not available. Therefore, the variance for the comparator outcomes was imputed using methodology outlined in the Cochrane Handbook.[78] The CIs for comparators were imputed from the CIs of the adjusted netarsudil-latanoprost outcomes from the STC.[78] The CIs of the comparator were estimated by subtracting the mean weighted outcomes of netarsudil-latanoprost ($Mean_{SZC}$) from the lower and upper CIs, and adding the difference to the mean comparator outcome respectively as reported in Equation 2.

Equation 2: Imputation of comparator CIs

$$LCI_{CPS} = Mean_{CPS} + (LCI_{SZC} - Mean_{SZC})$$
$$UCI_{CPS} = Mean_{CPS} + (UCI_{SZC} - Mean_{SZC})$$

The mean difference in percentage change in IOP between netarsudil-latanoprost and comparator arms was estimated using the formula in Equation 3. The estimate of the SE of the estimate's treatment effect was calculated using the formula in Equation 4.[79]

Equation 3: Estimation of treatment effect

$$Mean\ difference\ in\ \%\ change\ in\ IOP = \mu\ \%change_{intervention} - \mu\ \%change_{comparator}$$

Equation 4: Estimation of variance of the treatment effect

$$SE_{ITC} = \sqrt{SE_{intervention}{}^2 + SE_{comaprator}{}^2}$$

B.2.9.3.3 Covariates selection

Covariates for use in the STC were consistent with those used for the MAIC: age at baseline (mean in years) and baseline IOP (mean in mmHg). The selection process for covariates is described in section B.2.9.2.3.

B.2.9.3.4 Results

The coefficients and p-values from the linear regression models using each study population are shown in Table 25.

Table 25: Coefficients and p-values from linear regression model

Population used for model	Coefficient (SE; p-value)		
	Intercept	Age	IOP at baseline
Kozobolis *et al*. (2017) (dorzolamide-timolol)	[redacted]	[redacted]	[redacted]
Kozobolis *et al*. (2017) (brinzolamide-brimonidine)	[redacted]	[redacted]	[redacted]
ODLASER (brimonidine-timolol)	[redacted]	[redacted]	[redacted]

Abbreviations: SE – Standard error

The comparator absolute mean differences produced by the STC are listed in Table 26. Two sets of results were produced depending on the time point of data in each of the trials, to maximise the data input whilst managing for heterogeneity in reporting. The time points listed refer to the ODLASER, MERCURY 3, and Kozobolis *et al.* trials, respectively.

Table 26: STC output - Comparator absolute mean differences

Time point*	Week 8, 12, and 12		Week 8, 8, and 8	
Comparator	**Treatment effect of percentage change in IOP**	**SE of treatment effect**	**Treatment effect of percentage change in IOP**	**SE of treatment effect**
Dorzolamide-timolol	NA	NA	[redacted]	[redacted]
Brimonidine-timolol	[redacted]	[redacted]	[redacted]	[redacted]
Brinzolamide-brimonidine	[redacted]	[redacted]	[redacted]	[redacted]

Grey cells specify which data were not used in the base case; white cells maximise the evidence input whilst managing for heterogeneity in reporting.

*This row specifies from what time point, besides baseline, data from ODLASER, MERCURY 3, and Kozobolis were taken from, respectively.

Netarsudil-latanoprost data were taken from MERCURY 3; brimonidine-timolol data were taken from ODLASER; dorzolamide-timolol and brinzolamide/brimonidine data were taken from Kozobolis *et al*. (2017).

Abbreviations: IOP - Intraocular pressure; NA - Not available; SE - Standard error; STC - Simulated treatment comparison

B.2.9.3.5 Limitations

The STC represents a robust source of comparative effectiveness for the patient population of interest to this appraisal, aiming to adjust where feasible, for cross-study differences in patient characteristics and manage the lack of comparator data.

As with the limitations raised in the MAIC in section B.2.9.2.5 above, variation in baseline characteristics poses a problem in the reliability of the STC output. Study eye diagnosis (POAG or OHT) was comparable in the ODLASER and Kozobolis *et al.* trials, but MERCURY 3 differed by including OHT patients, reflecting a variation in inclusion criteria across the studies. An STC may also produce biased estimates when extrapolating beyond the range of the IPD available if there is no overlap between populations, and the true covariate-outcome relationship is nonlinear outside of the range of the IPD, as only a linear relationship is accounted for.

As described in section B.2.9.2.5, some variation in previous treatments was present between studies. However, this discrepancy is not likely to bias the STC results, as patients across the three trials had similar topical therapy history, and surgery criteria were equivalent, ensuring patients were at a similar stage in the treatment pathway and in disease severity.

An STC requires much stronger assumptions than an anchored comparison, for instance that all important prognostic and effect modifiers can be accounted for. Due to limitations in the data reported in the comparator datasets (as was the case for the unanchored MAIC), it was not possible to adjust for all imbalances in the important prognostic factors and treatment effect modifiers identified by the UK clinical expert. Specifically, visual field mean deviation, corneal thickness, and family history of glaucoma were not reported in the comparator datasets and therefore could not be adjusted for. Other characteristics which were not considered critical, but may have improved the analysis, included cup to disc haemorrhages, baseline visual field indices, retinal nerve fibre layers, and corneal hysteresis. In addition, it is not possible to compare the cohorts for these baseline characteristics and thus, it is difficult to assess how differences, if any, may impact the results.

There is precedent for the use of an STC in ocular HTAs; the approach has been submitted to and accepted by NICE, most recently in the evaluation of dexamethasone intravitreal implant (TA824) for the treatment of diabetic macular oedema, for which a STC was conducted.[67]

In conclusion, though some limitations are present with the use of an STC, the method allows use of the whole netarsudil-latanoprost data whilst the MAIC reduces the ESS to small numbers, indicating unstable results. As such, the STC represents a robust estimation of the comparative treatment effectiveness of netarsudil-latanoprost versus relevant comparators and is used in the base case for this appraisal in section B.3.9. To further understand uncertainty in the estimates, both the MAIC and naïve comparison are included as sensitivity analyses.

B.2.10 Adverse reactions

B.2.10.1 Exposure

The extent of exposure in the MERCURY 3 trial was lower in the netarsudil-latanoprost group compared to the bimatoprost-timolol group.[53] Mean exposure (days ± SD) in the safety population was [redacted] days in the netarsudil-latanoprost group (n=218) and [redacted] days in the bimatoprost-timolol group (n=212). The median exposure was [redacted]

days in the netarsudil-latanoprost group compared to [redacted] days in the bimatoprost-timolol group.

B.2.10.2 Summary of TEAEs

Table 27 displays an overall summary of TEAEs occurring in the safety population of MERCURY 3. A total of [redacted]% of subjects in the netarsudil-latanoprost group and [redacted]% in the bimatoprost-timolol group experienced at least one TEAE. No serious treatment-related TEAEs (defined as reported as possibly related to the study drug) were reported in the netarsudil-latanoprost group, with ocular TEAEs being generally mild to moderate.[80] There were no clinically relevant differences reported between the treatment groups for ocular parameters or systemic parameters.

Table 27: Overall summary of treatment-emergent AEs by treatment group in MERCURY 3 – safety population

	Netarsudil-latanoprost QD (N = 218), n (%)	**Bimatoprost-timolol QD (N = 212), n (%)**
Number of TEAEs	483	290
Number of subjects with ≥1 TEAE	[redacted]	[redacted]
Number of ocular TEAEs	352	131
Number of subjects with ≥1 ocular TEAE	131 (60.1)	64 (30.2)
Number of non-ocular TEAEs	131	159
Number of subjects with ≥1 non-ocular TEAE	69 (31.7)	75 (35.4)
Number of serious TEAEs	8	10
Number of subjects with ≥1 serious TEAE	7 (3.2)	7 (3.3)
Number of treatment-related TEAEs*	291	91
Number of subjects with ≥1 treatment-related TEAE*	120 (55.0)	53 (25.0)
Number of treatment-related serious TEAEs*	0	0
Number of subjects with ≥1 serious treatment-related TEAE*	0 (0.0)	0 (0.0)
Number of subjects with TEAEs by maximum severity: Mild Moderate Severe Unknown/missing	 64 (29.4) 74 (33.9) 15 (6.9) [redacted]	 65 (30.7) 35 (16.5) 10(4.7) [redacted]
Number of subjects with TEAEs resulting in discontinuation of test agent	[redacted]	[redacted]
Number of subjects with TEAEs resulting in death	[redacted]	[redacted]

Source: MERCURY 3 CSR[53]

*Treatment-related TEAEs were defined as reported as possibly related to related to the study drug.[80]

Abbreviations: QD – Once daily; TEAE – Treatment-emergent adverse event.

B.2.10.3 Frequency of TEAEs

Table 28 shows the ocular TEAEs reported in ≥1% of subjects in the safety population.[53] The most common ocular TEAE was conjunctival hyperaemia, with an incidence of 33.0% in the netarsudil-latanoprost group, compared to 10.8% in the bimatoprost-timolol group. Cornea verticillata and conjunctival haemorrhage were the next most commonly-reported ocular TEAEs, and were also observed at a higher incidence in the netarsudil-latanoprost group (11.0% and 8.3%, respectively) compared to the bimatoprost-timolol group (0.0% and 2.4%, respectively). The [redacted] of hyperaemia experienced by patients in the netarsudil-latanoprost group may be due to the vasodilatory effect of rho-associated protein kinase inhibitors compared with the inflammatory allergic type typically experienced by bimatoprost-timolol patients. Haemorrhages in netarsudil-latanoprost patients observed may also be due to the vasodilatory effect and would not cause visual changes or patient disturbances.

Table 28: Ocular TEAEs occurring at an incidence of ≥1% in MERCURY 3 – safety population

	Netarsudil-latanoprost QD (N=218), n (%)	**Bimatoprost-timolol QD (N=212), n (%)**
Any TEAE	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]
Conjunctival hyperaemia	72 (33.0)	23 (10.8)
Cornea verticillata	24 (11.0)	0 (0.0)
Conjunctival haemorrhage	18 (8.3)	5 (2.4)
Eye pruritus	17 (7.8)	4 (1.9)
Punctate keratitis	12 (5.5)	5 (2.4)
Dry eye	[redacted]	[redacted]
Eye irritation	[redacted]	[redacted]
Conjunctivitis allergic	12 (5.5)	1 (0.5)
Foreign body sensation in eyes	[redacted]	[redacted]
Blurred vision	[redacted]	[redacted]
Blepharitis	[redacted]	[redacted]
Conjunctival oedema	[redacted]	[redacted]
Erythema of eyelid	[redacted]	[redacted]
Eye pain	[redacted]	[redacted]
Eyelid oedema	[redacted]	[redacted]
Visual acuity reduced	[redacted]	[redacted]
Abnormal sensation in eye	[redacted]	[redacted]
Conjunctival irritation	[redacted]	[redacted]
Eye allergy	[redacted]	[redacted]
Eyelids pruritus	[redacted]	[redacted]

Growth of eyelashes	[redacted]	[redacted]
Lacrimation increased	[redacted]	[redacted]
Ocular hyperaemia	[redacted]	[redacted]
Visual impairment	[redacted]	[redacted]
Keratitis	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Instillation site pain	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Vital dye staining cornea present	[redacted]	[redacted]
IOP increased	[redacted]	[redacted]

Source: MERCURY 3 CSR[53]

Abbreviations: IOP – Intraocular pressure; QD – Once daily; TEAE – Treatment-emergent adverse event.

Table 29 shows the systemic TEAEs reported in ≥1% of subjects in the safety population.[53] The most common type of systemic TEAE was [redacted], with an incidence of [redacted]% in the netarsudil-latanoprost group, compared to [redacted]% in the bimatoprost-timolol group.[53] [redacted] were the next most commonly-reported systemic TEAE, and were observed at a higher incidence in the netarsudil-latanoprost group ([redacted]%) compared to the bimatoprost-timolol group ([redacted]%). In the netarsudil-latanoprost group and the bimatoprost-timolol group, [redacted] % and [redacted] % of patients experienced [redacted], respectively.

Table 29: Systemic TEAEs occurring at an incidence of ≥1% in MERCURY 3 – safety population

	Netarsudil-latanoprost QD (N=218), n (%)	**Bimatoprost-timolol QD (N=212), n (%)**
Vascular disorders	[redacted]	[redacted]
Hypertension	10 (4.6)	17 (8.0)
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Hypertriglyceridemia	[redacted]	[redacted]
Hyperlipidaemia	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]

Nervous system disorders	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Cholelithiasis	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]

Source: MERCURY 3 CSR[53]

Abbreviations: QD – Once daily; TEAE – Treatment-emergent adverse event.

B.2.10.4 TEAEs by severity

Table 30 shows the ocular TEAEs occurring at an incidence of ≥5% in the safety population, graded by severity.[53] TEAEs in the eye disorders system organ class (SOC) were graded as mild in [redacted], moderate in [redacted], and severe in [redacted] of those subjects in the netarsudil-latanoprost group. In the bimatoprost-timolol group, [redacted] were graded as mild, moderate in [redacted], and severe in [redacted]. The incidences of mild, moderate and severe conjunctival hyperaemia were [redacted] in the netarsudil-latanoprost group. The incidences of mild and moderate cornea verticillata and conjunctival haemorrhage were also [redacted] in the netarsudil-latanoprost group compared to the bimatoprost-timolol group. In both treatment groups, there were [redacted] incidences of severe cornea verticillata or conjunctival haemorrhage.

Table 30: Severity of ocular TEAEs occurring at an incidence of ≥5% in MERCURY 3, by maximum severity – safety population

	Netarsudil-latanoprost QD (N=218), n (%)	**Bimatoprost-timolol QD (N=212), n (%)**
Ocular TEAEs		
Eye disorders Mild n (%) Moderate n (%)	[redacted]	[redacted]

Severe n (%)	[redacted]	[redacted]
Conjunctival hyperaemia		
Mild n (%)	[redacted]	[redacted]
Moderate n (%)	[redacted]	[redacted]
Severe n (%)	[redacted]	[redacted]
Cornea verticillata		
Mild n (%)	[redacted]	[redacted]
Moderate n (%)	[redacted]	[redacted]
Severe n (%)	[redacted]	[redacted]
Conjunctival haemorrhage		
Mild n (%)	[redacted]	[redacted]
Moderate n (%)	[redacted]	[redacted]
Severe n (%)	[redacted]	[redacted]

Source: MERCURY 3 CSR[53]

Abbreviations: QD – Once daily; TEAE – Treatment-emergent adverse event.

B.2.10.5 Treatment-related TEAEs

Table 31 displays the ocular TEAEs occurring in ≥1% of subjects in the safety population.[53] A total of 55.0% (120/218) of subjects in the netarsudil-latanoprost group compared with 25.0% (53/212) of subjects in the bimatoprost-timolol group reported a treatment-related TEAE. Ocular AEs were the most commonly-reported TEAE during the study. The majority of ocular TEAEs were considered related to treatment and were reported at a higher incidence in the netarsudil-latanoprost group compared with the bimatoprost-timolol group ([redacted] vs. [redacted], respectively).

The incidence of non-ocular TEAEs was low in both treatment groups. There were no non-ocular treatment-related TEAEs occurring at an incidence ≥1% in any treatment group.

Table 31: Treatment-related TEAEs occurring in ≥1% of subjects in any treatment group in MERCURY 3 – safety population

	Netarsudil-latanoprost QD (N=218), n (%)	Bimatoprost-timolol QD (N=212), n (%)
Any TEAE	**120 (55.0)**	**53 (25.0)**
Eye disorders	[redacted]	[redacted]
Conjunctival hyperaemia	[redacted]	[redacted]
Cornea verticillata	[redacted]	[redacted]
Eye pruritus	[redacted]	[redacted]
Punctate keratitis	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]
Eye irritation	[redacted]	[redacted]
Conjunctival haemorrhage	[redacted]	[redacted]
Foreign body sensation in eyes	[redacted]	[redacted]
Conjunctival oedema	[redacted]	[redacted]

Erythema of eyelid	[redacted]	[redacted]
Eyelid oedema	[redacted]	[redacted]
Blurred vision	[redacted]	[redacted]
Eye pain	[redacted]	[redacted]
Abnormal sensation in eye	[redacted]	[redacted]
Blepharitis	[redacted]	[redacted]
Conjunctival irritation	[redacted]	[redacted]
Growth of eyelashes	[redacted]	[redacted]
Ocular hyperaemia	[redacted]	[redacted]
Visual acuity reduced	[redacted]	[redacted]
Eye allergy	[redacted]	[redacted]
Eyelids pruritus	[redacted]	[redacted]
Lacrimation increased	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Instillation site pain	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Vital dye staining cornea present	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]

Source: MERCURY 3 CSR[53]

Abbreviations: QD – Once daily; TEAE – Treatment-emergent adverse event.

The most common ocular TEAE across both the netarsudil-latanoprost and bimatoprost-timolol treatment groups was conjunctival hyperaemia. Table 32 shows the proportion of subjects with treatment-emergent conjunctival hyperaemia by consecutive visit. The majority of cases of conjunctival hyperaemia were predominantly mild to moderate in severity (Table 30). Despite that, conjunctival hyperaemia was the most common ocular TEAE. The mean duration to resolve the adverse event was relatively small across treatment arms, ranging between [redacted] and [redacted] days in the bimatoprost-timolol and netarsudil-latanoprost treatment groups, respectively (Table 33).

As conjunctival hyperaemia was the most common ocular TEAE, sub-analyses were conducted in MERCURY 3 for this event. These included a comparison of the proportion of patients with a one severity grade increase from baseline to day 15 and day 90; a comparison of the percentage of patients who had a finding judged to be clinically significant by region, finding, time point and eye; and continuous summary statistics were provided for the change from baseline at each visit.

In the first test, a [redacted] was observed in the Fisher test comparing netarsudil-latanoprost and bimatoprost-timolol for all time points, whilst in the second test, [redacted] for all time points post-visit 3.

Table 32: Proportion of subjects with treatment-emergent conjunctival hyperaemia in MERCURY 3, by number of consecutive visits – safety population

	Netarsudil-latanoprost QD (N=218), n (%)	Bimatoprost-timolol QD (N=212), n (%)
Subjects with treatment-emergent conjunctival hyperaemia (m) by number of consecutive visits	**72.0 (33.0)**	**23.0 (10.8)**
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]

Source: MERCURY 3 CSR[53]

Abbreviations: QD – Once daily.

Note: m is the number of subjects with treatment-emergent conjunctival hyperaemia in a given treatment group for the population analysed. Subjects with the event that did not cover any visit are counted in visit 0.

Table 33: Duration of resolved events of conjunctival hyperaemia

Treatment group	N	Mean duration of resolved AEs (days)	SD	Minimum	Median	Maximum
Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: MERCURY 3 sub-analysis – conjunctival hyperaemia[81]

Abbreviations: AE – Adverse event; SD – Standard deviation

B.2.10.6 Serious TEAEs

Table 34 shows the reported serious adverse events (SAEs) in the safety population. A total of 14 out of 430 subjects experienced a SAE across both treatment groups; none were considered to be related to treatment. A total of 3.2% of SAEs were in the netarsudil-latanoprost group and 3.3% were in the bimatoprost-timolol group. All SAEs reported during the treatment period were non-ocular SAEs.

Table 34: Serious adverse events in MERCURY 3 – safety population

	Netarsudil-latanoprost QD (N=218), n (%)	Bimatoprost-timolol QD (N=212), n (%)
Any serious TEAEs	**7 (3.2)**	**7 (3.3)**
Hepatobiliary disorders	**3 (1.4)**	**0 (0.0)**
Cholecystitis	2 (0.9)	0 (0.0)
Cholecystitis acute	1 (0.5)	0 (0.0)
Gastrointestinal disorders	**2 (0.9)**	**0 (0.0)**

	Netarsudil-latanoprost QD (N=218), n (%)	Bimatoprost-timolol QD (N=212), n (%)
Enteritis	1 (0.5)	0 (0.0)
Pancreatitis	1 (0.5)	0 (0.0)
Injury, poisoning and procedural complications	**0 (0.0)**	**2 (0.9)**
Accidental poisoning	0 (0.0)	1 (0.5)
Road traffic accident	0 (0.0)	1 (0.5)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**1 (0.5)**	**1 (0.5)**
Metastases to lung	0 (0.0)	1 (0.5)
Transitional cell carcinoma	1 (0.5)	0 (0.0)
Nervous system disorders	**0 (0.0)**	**2 (0.9)**
Facial paralysis	0 (0.0)	1 (0.5)
Ischemic stroke	0 (0.0)	1 (0.5)
Cardiac disorders	**0 (0.0)**	**1 (0.5)**
Cardiac failure	0 (0.0)	1 (0.5)
Congenital, familial and genetic disorders	**0 (0.0)**	**1 (0.5)**
Dermoid cyst	0 (0.0)	1 (0.5)
Endocrine disorders	**1 (0.5)**	**0 (0.0)**
Inappropriate antidiuretic hormone secretion	1 (0.5)	0 (0.0)
Infections and infestations	**0 (0.0)**	**1 (0.5)**
Lower respiratory tract infection	0 (0.0)	1 (0.5)
Pneumonia	0 (0.0)	1 (0.5)
Renal and urinary disorders	**0 (0.0)**	**1 (0.5)**
Renal failure	0 (0.0)	1 (0.5)
Surgical and medical procedures	**1 (0.5)**	**0 (0.0)**
Umbilical hernia repair	1 (0.5)	0 (0.0)

Source: MERCURY 3 CSR[53]

Abbreviations: QD – Once daily; TEAE – Treatment-emergent adverse event.

B.2.10.7 Discontinuation due to TEAEs

[redacted] in the bimatoprost-timolol group ([redacted]) discontinued treatment due to TEAEs than in the netarsudil-latanoprost group ([redacted]).[53] Of the most commonly-reported TEAEs, [redacted].

Table 35 shows the number and percentage of subjects who discontinued study medication and the study due to an adverse event.

Table 35: Number and percentage of subjects with AEs resulting in study treatment discontinuation in MERCURY 3, by treatment group - safety population

	Netarsudil-latanoprost QD (N=40), n (%)	Bimatoprost-timolol QD (N=4), n (%)	All subjects (N=44), n (%)
Any TEAEs resulting in test agent discontinuation	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]
Conjunctival hyperaemia	[redacted]	[redacted]	[redacted]
Conjunctivitis allergic	[redacted]	[redacted]	[redacted]
Cornea verticillata	[redacted]	[redacted]	[redacted]
Eye allergy	[redacted]	[redacted]	[redacted]
Conjunctival oedema	[redacted]	[redacted]	[redacted]
Foreign body sensation in eyes	[redacted]	[redacted]	[redacted]
Conjunctival irritation	[redacted]	[redacted]	[redacted]
Eye irritation	[redacted]	[redacted]	[redacted]
Eye pruritus	[redacted]	[redacted]	[redacted]
Visual acuity reduced	[redacted]	[redacted]	[redacted]
Blepharitis	[redacted]	[redacted]	[redacted]
Corneal opacity	[redacted]	[redacted]	[redacted]
Eye discharge	[redacted]	[redacted]	[redacted]
Optic ischemic neuropathy	[redacted]	[redacted]	[redacted]
Punctate keratitis	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]	[redacted]
Lower respiratory tract infection	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Blood magnesium decreased	[redacted]	[redacted]	[redacted]
Vital dye staining cornea present	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]	[redacted]
Inappropriate antidiuretic hormone secretion	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Instillation site pain	[redacted]	[redacted]	[redacted]

	Netarsudil-latanoprost QD (N=40), n (%)	Bimatoprost-timolol QD (N=4), n (%)	All subjects (N=44), n (%)
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]
Alkalosis	[redacted]	[redacted]	[redacted]
Hyponatremia	[redacted]	[redacted]	[redacted]
Hypophosphatemia	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]	[redacted]
Oliguria	[redacted]	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]	[redacted]
Renal tubular necrosis	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Stridor	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Eczema	[redacted]	[redacted]	[redacted]

Source: MERCURY 3 CSR[53]

Abbreviations: QD – Once daily; TEAE – Treatment-emergent adverse event.

Note: n is the number of subjects with at least one adverse event; % is based on the number of subjects (N) in a given treatment group for the population being analysed.

When reporting incidence, a subject will only be counted once if they ever experience an event within the SOC or individual PT.

B.2.10.8 Deaths

One death was reported during the study in the bimatoprost-timolol group [redacted].

B.2.11 Ongoing studies

There are no ongoing studies that will provide additional evidence in the next 12 months for the indication being appraised.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings

B.2.12.1.1 MERCURY 3 efficacy evidence

Compared to bimatoprost-timolol, netarsudil-latanoprost demonstrated clinical non-inferiority in the ITT population for the primary efficacy endpoint (mean IOP at specified time points at week 2, week 6 and month 3) in MERCURY 3; the upper limit of the 95% CIs around the difference in IOP were ≤1.5 mmHg at all time points and ≤1.0 mmHg at the majority (6 out of 9) of time points from week 2 through to month 3.[53]

Netarsudil-latanoprost demonstrated clinical non-inferiority relative to bimatoprost-timolol in the ITT population for the mean diurnal IOP at each post-treatment visit and showed a consistent reduction in IOP at post-treatment time points.[53] Despite the mean percent change from diurnally adjusted baseline IOP being numerically greater in the bimatoprost-timolol group compared to the netarsudil-latanoprost group, there was no statistically significant difference between the treatment groups at the majority of time points.

[redacted].[53] An analysis of the SF-36 physical component summary with the elevation rule where an increased significance level of 15% was applied showed that netarsudil-latanoprost had a considerable significant advantage in preventing worsening quality of life in the ITT population.[82]

Based on these results reported in the MERCURY 3 trial, netarsudil-latanoprost represents a clinically innovative alternative treatment option for the management of adults with POAG or OHT, whose IOP has not improved with previous treatment in the UK.

B.2.12.1.2 MERCURY 3 safety evidence

In MERCURY 3, the safety profile of [redacted]; mostly mild to moderate ocular TEAEs; no serious treatment-related TEAEs; and [redacted].[53] Higher incidence of at least one TEAE compared to the bimatoprost-timolol QD group was observed, however the impact of these is limited and can in part be described by the mechanism of action of netarsudil-latanoprost, as described below.

The most common ocular AEs were conjunctival hyperaemia, cornea verticillata and conjunctival haemorrhage; a higher incidence of each of these AEs was observed in the netarsudil-latanoprost group compared to the bimatoprost-timolol group.[53] The higher rate of hyperaemia experienced by patients in the netarsudil-latanoprost group may be due to the vasodilatory effect of rho-associated protein kinase inhibitors compared with the inflammatory allergic type typically experienced by bimatoprost-timolol patients.[83] Haemorrhages in netarsudil-latanoprost patients observed may also be due to the vasodilatory effect and would not cause visual changes or patient disturbances. Furthermore, MERCURY 3 excluded patients who were known to be non-responders to bimatoprost-timolol or who showed insufficient tolerability to bimatoprost-timolol from entering the trial, thereby excluding such patients from the bimatoprost-timolol treatment group; this is a likely reason for the higher incidence of ocular AEs observed in the netarsudil-latanoprost treatment group compared to the bimatoprost-timolol group. A UK clinical expert advised that from a clinical perspective, the potential local and ocular side-effects of netarsudil-latanoprost (conjunctival hyperaemia,

cornea verticillata and conjunctival haemorrhage) have limited clinical relevance. These local and ocular side-effects were considered as mild and manageable, particularly compared to systemic AEs.[84] Netarsudil-latanoprost can therefore be considered a safe and innovative treatment option for patients with POAG or OHT that are underserved by current treatment options.

The most common systemic AEs were [redacted]. [53] [redacted] were the next most commonly-reported systemic TEAE, and were observed at a higher incidence in the netarsudil-latanoprost group ([redacted]%) compared to the bimatoprost-timolol group ([redacted]%).

Real-world data from the use of netarsudil-latanoprost in Germany has demonstrated that the rate of associated AEs are a lot lower in this setting, compared to what was observed in MERCURY 3.[85] Since December 2022, over [redacted] doses have been sold in Germany, and only [redacted] non-serious cases of AEs have been reported associated with the use of netarsudil-latanoprost, which have mainly consisted of [redacted] and [redacted]. Furthermore, the Committee for Medicinal Products for Human Use (CHMP) consider that the safety of netarsudil-latanoprost has been sufficiently demonstrated.[58] The extension of the PSUR frequency of netarsudil-latanoprost from 6 months to 1 year was granted by the EMA on 12 January 2023, showing that netarsudil-latanoprost has a favourable and consistent safety profile.

Netarsudil-latanoprost is the only PGA-containing FDC that does not contain a beta blocker. Beta blocker-containing ocular agents are associated with systemic side-effects and need to be cautiously prescribed in patients with contraindications, such as respiratory diseases and underlying cardiovascular conditions.[86] Therefore, netarsudil-latanoprost will provide an alternative treatment option for patients in whom beta-blockers are contraindicated or not tolerated. This could provide patients intolerant to beta blocker-containing ocular agents with an alternative treatment, that they could remain on for a lifetime duration, avoiding treatment switching.

B.2.12.1.3 Comparative efficacy via an ITC

Due to data availability, an NMA using a connected network was not possible. Therefore, to understand the uncertainty around comparative treatment effectiveness, a variety of unanchored ITC methods were carried out; namely, MAIC, STC, and a naïve comparison.

An unanchored MAIC was conducted, using IPD from MERCURY 3 and aggregate data from the brimonidine-timolol arm of ODLASER and the brinzolamide-brimonidine and dorzolamide-timolol treatment arms of Kozobolis *et al*. (2017), adjusting for the two feasible prognostic factors and treatment effect modifiers identified by a UK clinical expert (age and IOP). However, the robustness of the unanchored MAIC outcomes is weak based on the limitations resulting from the small ESS' after weighting of the MERCURY 3 IPD, indicating that results may be unstable.

Thus, an STC for the percentage reduction in diurnal IOP from baseline of netarsudil-latanoprost (MERCURY 3) to the three FDC comparators was preferred to inform the base-case cost-effectiveness analysis. The STC showed a [redacted], respectively).

As described in section B.2.9.3.5, certain factors may limit the reliability of comparative efficacy estimates derived from a STC, for instance, variation in the baseline characteristics between the clinical trials being compared. One key difference between MERCURY 3 and the comparator studies was the inclusion of patients with OHT in MERCURY 3; patients with OHT were excluded from the ODLASER and Kozobolis *et al*. (2017) trials. An STC may also produce biased estimates when extrapolating beyond the range of the IPD available if there is no overlap between populations, and the true covariate-outcome relationship is nonlinear outside of the range of the IPD, as only a linear relationship is accounted for.

An STC requires much stronger assumptions than an anchored comparison, for instance that all important prognostic and effect modifiers can be accounted for. Due to limitations in the data reported in the comparator datasets (as was the case for the unanchored MAIC), it was not possible to adjust for all imbalances in the important prognostic factors and treatment effect modifiers identified by the UK clinical expert. Furthermore, it was not possible to assess for heterogeneity between the cohorts for the unreported baseline characteristics and thus, it is difficult to assess how differences, if any, may impact the reliability of the results.

B.2.12.2 Strengths and limitations

B.2.12.2.1 Strengths of the evidence base

MERCURY 3, a phase 3, double-blinded, randomised, multicentred trial, was the only clinical trial identified for netarsudil-latanoprost, whose comparator was a FDC.[53] The results of the MERCURY 3 trial are relevant to the decision problem specified in the NICE final scope, proposing the use of netarsudil-latanoprost for patients with POAG or OHT whose IOP has not improved after treatment with a prostaglandin or netarsudil (i.e., those eligible for FDCs).[87]

The external validity and generalisability of the MERCURY 3 trial to UK clinical practice is supported by:

- **Population**: all patients in the MERCURY 3 trial had received previous treatment for POAG or OHT; the ophthalmic exclusion criteria excluded patients that were treatment naïve.[53] Patients in MERCURY 3 were adults (aged 18 or older) and had a diagnosis of OAG or OHT in both eyes. Thus, the results of the MERCURY 3 trial provide robust evidence to support the use of netarsudil-latanoprost in the patient population specified in the decision problem. In addition, MERCURY 3 was a multicentre, international study and patients were enrolled across 12 UK trial sites, making this trial generalisable to the UK population of patients with previously treated POAG or OHT.

- **Intervention**: netarsudil-latanoprost was evaluated in line with its licensed indication (adult patients with POAG or OHT for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction).[58]

- **Comparators**: netarsudil-latanoprost was evaluated in comparison to bimatoprost-timolol.[53] This is in line with the expectation that the NICE-recommended population for netarsudil-latanoprost will reflect the license wording and be limited to the reduction of elevated IOP in adult patients with POAG or OHT for whom monotherapy with a PGA or netarsudil provides insufficient IOP reduction (i.e., those eligible for FDCs).[58]

- **Outcomes**: all the key outcomes relevant for decision making were assessed in the MERCURY 3 trial (mean IOP, visual acuity, visual field test, evaluation of anterior and posterior segment parameters, structural integrity of the optic nerve, adverse effects of treatment and health-related quality-of-life [HRQoL]).[87] The following outcomes were

used in the economic analysis: mean IOP (specifically, percentage reduction in IOP from baseline), adverse effects of treatment and HRQoL.

No severe AEs were experienced by ≥5% patients in the netarsudil-latanoprost arm, the standard threshold considered relevant for including AEs within economic modelling. Similar levels of severe AEs were seen across the treatment arms (3.2% and 3.3% in the netarsudil-latanoprost and bimatoprost-timolol arms, respectively).[53] Consequently, AEs of all grades (1+) were included in the model detailed in section B.3.

The STC method used to inform base-case comparative treatment effectiveness allowed use of data from most patients in the netarsudil-latanoprost arm of MERCURY 3, while adjusting for differences in baseline prognostic variables and treatment effect modifiers. Diagnostic tests demonstrated that the STC method performed well and therefore results from this comparison can be considered robust. To understand the uncertainty around these estimates, both the MAIC and naïve comparison are also presented in this submission.

B.2.12.2.2 Limitations of the evidence base

In addition to MERCURY 3, the SLR identified three RCTs that included a FDC as an intervention or comparator.[61–63] Due to limited data availability and reporting, comparative evidence could only be generated for comparisons of netarsudil-latanoprost to brimonidine-timolol, brinzolamide-brimonidine and dorzolamide-timolol. This is considered as a limitation, as comparative efficacy could not be generated for other FDCs that are included in the economic analysis.

In both FDC comparator trials included in the ITC analyses, (ODLASER and Kozobolis *et al*. [2017]), the patient populations were small.[61,62] This represents a key challenge when attempting to derive the comparative efficacy data of netarsudil-latanoprost versus the three FDCs. Hence, whilst performing an unanchored MAIC improved the comparability of the trial populations, it dramatically reduced the ESS' of the weighted MERCURY 3 IPD. Hence, the MAIC results were deemed to have limited robustness and an STC approach was preferred in the base case of the economic analysis.

Furthermore, the comparator FDC trials included patients with POAG only – patients with OHT were excluded.[61,62] Therefore, the study populations of ODLASER and Kozobolis *et al*. (2017) do not fully align with the patient population specified in the netarsudil-latanoprost decision problem, or the patient population in the MERCURY 3 trial. However, sensitivity analyses were conducted as part of the ITCs assess the clinical effect in patients with OHT, by reweighting the MERCURY 3 IPD.

Several baseline characteristics, key prognostic factors and treatment effect modifiers were not available in one or more of the clinical trials. This impacted the assessment of population comparability and the feasibility of ITCs. Due to the limited reporting of all key prognostic factors and treatment effect modifiers, only two covariates (age and IOP) were feasible for inclusion in the ITCs. The two safety outcomes of interest (DDTAE and incidence of AEs) were not reported in the FDC comparator trials and hence, comparative efficacy could not be generated against netarsudil-latanoprost for these outcomes.

Despite these limitations in the evidence base, the company has made efforts to include all available relevant comparator data and adjust for differences in prognostic variables and treatment effect modifiers.

B.2.12.3 Conclusion

As described in section B.1.3.1, the TM is responsible for approximately 70-96% of AH outflow, which is one of the main mechanisms to control IOP.[2–4] Currently available topical treatments for glaucoma do not act directly on the TM to reduce IOP, highlighting an important unmet need. Netarsudil-latanoprost has a novel mechanism of action, as the first topical treatment for POAG/OHT that targets the TM pathway to increase AH outflow and hence reduce IOP. Additionally, only one drop of treatment needs to be applied in the affected eye(s) per day, which will support patient adherence to treatment and reduce the chances of missed doses compared to treatments requiring more than one drop daily, which is typical especially for patients who are intolerant of beta-blockers. Netarsudil-latanoprost will also be suitable for patients already using all tolerable currently available glaucoma medications and remain sub-optimally controlled, avoiding substantial risks associated with surgery.

Netarsudil-latanoprost demonstrated clinical non-inferiority versus bimatoprost-timolol for the primary endpoint in the ITT population of the MERCURY 3 trial, in patients with POAG or OHT whose IOP had not improved despite prior treatment.[53] The MERCURY 3 trial is the most robust source of evidence generalisable to the UK population for netarsudil-latanoprost.

Netarsudil-latanoprost exhibited a higher incidence of ocular AEs (conjunctival hyperaemia, cornea verticillata and conjunctival haemorrhage) compared to bimatoprost-timolol in MERCURY 3.[53] However, a UK clinical expert advised that these side-effects have limited clinical relevance and are considered as mild and manageable compared to systemic side-effects.[84] These AEs were resolved when the treatment was discontinued and no serious AEs were reported. Furthermore, real-world evidence from the use of netarsudil-latanoprost in Germany has demonstrated that the number of associated AEs is a lot lower in practice, compared to what was observed in MERCURY 3. In MERCURY 3, patients who were known to be non-responders or who showed insufficient tolerability to bimatoprost-timolol were excluded from the bimatoprost-timolol treatment group based on the inclusion and exclusion criteria of the trial; this is a likely reason for the higher incidence of ocular AEs observed in the netarsudil-latanoprost treatment group compared to the bimatoprost-timolol group.

Overall, netarsudil-latanoprost is a clinically effective treatment option with a novel mechanism of action, that can be an alternative treatment option for patients not only with POAG or OHT alone, but for patients with POAG or OHT in whom beta-blockers are contraindicated or not tolerated.

B.3 Cost-effectiveness

B.3.1 Published cost-effectiveness studies

An economic SLR was conducted to identify economic evidence for netarsudil-latanoprost and other interventions for the treatment of POAG or OHT in adults. The methodology undertaken is summarised in Appendix G. Database searches were performed in November 2022. The key objective of the SLR was to identify cost-effectiveness studies of therapies available for the treatment of POAG or OHT. The review question that was used to identify the studies was:

- What cost-effectiveness studies have been conducted for the treatment of OAG or OHT?

Full details of the search strategy, eligibility criteria applied, and references identified can be found in Appendix G. The economic SLR identified two relevant published sources, one of which reported results from two trials. A summary of the sources and data presented are presented in Table 36 below. No health technology appraisal (HTA) reports for therapies in POAG or OHT were identified.

Table 36: Summary list of published cost-effectiveness studies (n=2)

Study and section	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
Gazzard (2019a)[75] Chapter 4: Health economic decision model	2019	• SLT versus eyedrops • Markov state transition model • Health states: OHT, Glaucoma 'mild', Glaucoma 'moderate', Glaucoma 'severe', dead • 6-month cycle length and lifetime horizon	• Patients with a diagnosis of OAG or OHT with a decision to treat made by a consultant glaucoma specialist • Mean age: 63.1	• SLT: 12.5 QALYs • Eyedrops: 12.3 QALYs • Incremental QALYs: 0.2	• SLT: £17,541 • Eyedrops: £20,435 • Incremental costs: -£2,894	SLT dominating
Gazzard (2019a)[75] Chapter 3: Results	2019	• Trial-based cost-utility analysis of SLT versus eyedrops • Health and social care costs and QALYs were calculated for the within-trial period (3-years)	• Patients with untreated OAG or OHT in one or both eyes, qualified for treatment according to NICE guidelines and, for those with OAG, had visual field loss with mean deviation not worse than –12 dB in the better eye, or –15 dB in the worse eye and corresponding damage to the optic nerve • Mean age: 63.1	• SLT: 2.63 QALYs • Eyedrops: 2.61 QALYs • Incremental QALYs: 0.02	• SLT: £3,890 • Eyedrops: £3,993 • Incremental costs: -£103	SLT dominating
Gazzard (2019b)[88]	2019	• Trial-based cost-utility analysis of SLT	• Patients with untreated OAG or OHT in one or both eyes, qualified for treatment	• SLT: 2.65 QALYs • Eyedrops: 2.62 QALYs	• SLT: NR • Eyedrops: NR	NR (SLT dominating implied)

Study and section	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
		versus eyedrops • Health and social care costs and QALYs were calculated for the within-trial period (3-years)	according to NICE guidelines and, for those with OAG, had visual field loss with mean deviation not worse than –12 dB in the better eye, or –15 dB in the worse eye and corresponding damage to the optic nerve. • Mean age: 63.0 (weighted average of two treatment arms)	• Incremental QALYs: 0.024	• Incremental costs: -£205 (in SLT group) and -£465 (in eye drop group)	

Abbreviations: dB – Decibels; ICER – Incremental cost-effectiveness ratio; NICE – National Institute for Health and Care Excellence; NR – Not reported; OAG – Open-angle glaucoma; OHT– Ocular hypertension; QALY – Quality-adjusted life years; SLT – Selective laser trabeculoplasty

B.3.2 Economic analysis

Two publications were identified from the SLR described in section B.3.1, reporting three sets of cost-effectiveness analyses from the LiGHT RCT, comparing SLT versus eye drops as first-line treatment.[75,88] As such, neither publication reflects the decision problem for this appraisal. However, features of the cost-effectiveness analysis (CEA) are described below as they are the closest cost-effectiveness evidence to this decision problem available from the literature.

The identified cost-effectiveness analyses utilised a Markov state transition model structure with health states reflective of OHT and glaucoma status as defined by mean visual field defect, optic nerve health (healthy vs. glaucomatous optic neuropathy), and central scotoma on visual field, in accordance with Canadian IOP guidelines.[89] Gazzard (2019a)[75] and Gazzard (2019b)[88] reported the ICER for the within-trial period (36 months), whilst the expected costs and QALYs over a lifetime (a maximum of 30 years) were also reported in Gazzard (2019a)[75].

All the analyses considered a UK perspective, and demonstrated that SLT dominated eye drops, incurring positive incremental QALYs and negative incremental costs, over both the within-trial period and over a lifetime time horizon.

For this submission, a *de novo* Markov state transition model structure was employed, as described in the following sections.

B.3.2.1 Patient population

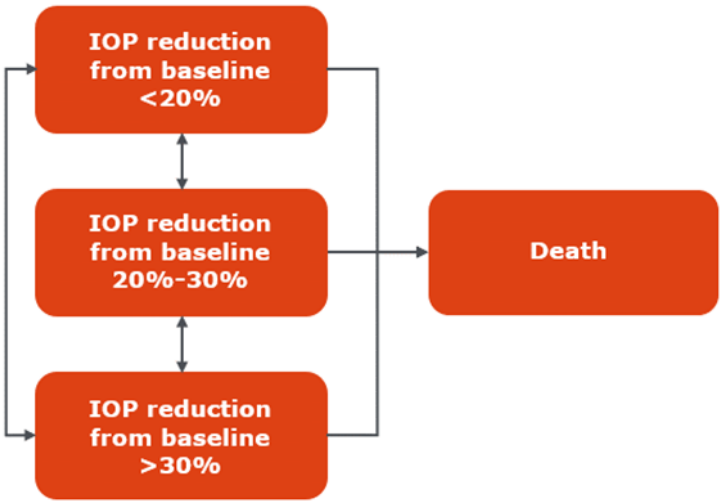
The population entering the model comprises of adult patients with POAG or OHT for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction, which is in line with the marketing authorisation for netarsudil-latanoprost.[87] This is also in alignment with the population considered in the decision problem (see section B.1.2) and that included in the MERCURY 3 trial. A sensitivity analysis is included in the model that removes OHT patients to align with the populations in the comparator trials (discussed further in section B.2.9).

B.3.2.2 Model structure

A *de novo* Markov state transition cohort structure was deemed most appropriate to capture the long-term, chronic nature of POAG and OHT, as per published models from the literature.[39,75,88] The model comprises of four health states, three of which are defined by percentage reductions in IOP from baseline, and an absorbing death state, as illustrated in Figure 14. The three health states are based on thresholds of <20%, 20-30%, and >30% reduction in IOP from baseline.

Patients enter the model in the 'IOP reduction from baseline <20%' health state, where they initiate treatment with either netarsudil-latanoprost or one of the comparator treatments. Whilst on treatment, patients can transition between any of the health states as described in Figure 14, based on their percentage reduction in IOP from baseline. Patients can enter the death state from any model health state. Patients can discontinue treatment at a constant rate per cycle, where the discontinuation rates applied for netarsudil-latanoprost and bimatoprost-timolol are taken from the MERCURY 3 trial, and the discontinuation rates for the remaining comparators are assumed equivalent to bimatoprost-timolol in the absence of data. When patients discontinue treatment in the model, they are removed from the model health states; discontinued patients do not incur costs or QALYs. This is reflective of clinical practice where discontinued patients will no longer accumulate costs and quality-of-life (QoL) benefits associated with treatment.

Figure 14: Markov model structure



Abbreviations: IOP – Intraocular pressure

A Markov state transition model structure was employed with health states focusing on IOP, which aligns with the model developed as part of NICE guideline 81 (NG81).[6] Long-term lowering of IOP remains the only strategy known to be effective against conversion to chronic OAG and sight loss, and control of IOP remains critical to current therapeutic approaches.[64] Additionally, NICE have identified IOP as a useful and conveniently measured 'surrogate outcome' for treatment success in glaucoma, with the aim of OAG treatment being to lower IOP, thus preserving visual function. As such, IOP was deemed the most suitable outcome from which to define health states reflective of the long-term goals of OAG and OHT treatment. The use of this measure aligns with the primary endpoint of the MERCURY 3 trial for netarsudil-latanoprost and was also validated by a UK clinical expert as being clinically appropriate. A *de novo* model was therefore developed based on IOP.

Clinically applicable target IOP ranges vary from patient to patient, dependent on the severity of their condition. As such, defining health states based on absolute IOP thresholds was deemed unsuitable for this analysis, as confirmed by a UK clinical expert.[90] Evidence from the published literature suggests that a greater IOP reduction is associated with greater reduction in disease progression, and therefore higher QoL and lower costs associated with treatment.[12] As such, the structure of the model was designed to capture these benefits, using health states defined by percentage change from baseline in IOP.

The choice of a Markov state transition cohort structure and the use of IOP to define health states was validated by a UK clinical expert.[90] The use of IOP health states was guided by the literature collected in the SLR and the primary endpoint in the MERCURY 3 trial.[53,75,88] To further support this, targeted literature searches were undertaken to inform the IOP threshold definitions. Four sources were identified (Stewart *et al*. [2006], Orme *et al*. [2010], Lin *et al*. [2014] and Gazzard *et al*. [2019]) which applied 20% and 30% IOP reduction thresholds as indicators of treatment success, preventing progression, and a typical treatment target.[75,91–93] Accordingly, thresholds of <20%, 20-30%, and >30% reduction in IOP were applied in the model and validated with a UK clinical expert, who confirmed its clinical relevance for predicting disease progression in POAG and OHT.[90] The thresholds applied in the model also align with the suggested upper limit of initial target IOP for each eye as per the Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of glaucoma, in the absence of UK-specific guidelines.[94]

The NICE reference case states that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long enough to reflect any difference in costs or outcomes between the medicines being compared.[95] Given the chronic nature of POAG and OHT, a lifetime time horizon was adopted for the analysis, reflected in a 33-year time horizon with the expectation that no patient can live beyond 100 years (as noted in section B.3.3.1, the starting age in the model is 67 years). The lifetime time horizon enables disease progression to be monitored over a patient's lifetime.

A one-month cycle length is applied in the model, to align with the time point of IOP data collection in MERCURY 3, and to provide sufficient granularity to reflect rapid IOP reductions as observed in the trial.[53] A half-cycle correction is applied, assuming patients transition between health states mid-way through a cycle. Total costs and QALYs are calculated based on the distribution of patients across all health states in each cycle. These are accumulated over the model time horizon to calculate total costs and QALYs for the cohorts from which incremental results and the cost per QALY are determined. In line with the NICE reference case, the model adopts a UK NHS and Personal Social Services (PSS) perspective, and costs and outcomes are discounted at 3.5% per annum.[95] A treatment waning effect was not applied in the model in line with existing models and literature.[39,75,92,93]

Table 37 summarises the features of the economic analysis for this appraisal with respect to the NICE reference case. As there are no completed NICE appraisals for any of the comparator treatments considered, the table focuses on the current appraisal of netarsudil-latanoprost only.

Table 37: Features of the economic analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (33 years)	NICE guidelines state that the time horizon must be long enough to sufficiently capture differences in costs and health outcomes.[95] The mean age of patients in the MERCURY 3 trial was 67.2 years. Therefore a lifetime time horizon of 33 years is suitable to capture outcomes, as it is assumed that all patients will be dead by the age of 100.[53] A lifetime time horizon was also used in existing models in the published literature (NICE NG81[96], Gazzard 2019[75]).
Cycle length	1 month (30.44 days)	This aligns with the MERCURY 3 trial, in which IOP was generally measured at monthly intervals.[53] Using a 1-month cycle length will allow for optimal granularity in model inputs and will enable reflection of rapid reductions in IOP from baseline, as observed in the MERCURY 3 trial. The exact value (30.44) is calculated by dividing the number of days in a

		year (365.25) by the number of months in a year (12).
Intervention(s)	Netarsudil/latanoprost 0.02%/0.005% (Roclanda) ophthalmic solution once daily	This aligns with final NICE scope.
Comparators	Direct comparators (topical eye drop FDCs): • Bimatoprost-timolol • Brinzolamide-timolol • Latanoprost-timolol • Tafluprost-timolol • Travoprost-timolol • Dorzolamide-timolol • Brimonidine-timolol • Brinzolamide-Brimonidine Add-on treatments: • SLT • Trabeculectomy	This aligns with the final NICE scope.
Discount rate for costs and outcomes	3.5%	This aligns with the NICE reference case.[95] The impact of alternative discount rates has been tested in sensitivity analyses.
Perspective	UK NHS and PSS	This aligns with NICE reference case, which considers all direct health effects for patients and carers (if applicable).[95]
Half-cycle correction	Yes	This is applied to avoid the assumption that transitions between health states happen at the end of each cycle only.
Source of clinical efficacy	MERCURY 3 informed the clinical efficacy for netarsudil-latanoprost and bimatoprost-timolol. An ITC and SLR were used to inform the clinical efficacy for the remaining FDC comparators.	Head-to-head data for netarsudil-latanoprost and bimatoprost-timolol is informed by the MERCURY RCT.[53] As no head-to-head data exists between netarsudil-latanoprost and the remaining FDCs, an ITC was required to inform the clinical efficacy parameters for these comparators.
Treatment waning effect	Not included	Aligns with existing published economic models and literature in this disease area.[39,75,92,93]
Source of utilities	MERCURY 3 SF-36 data	SF-36 was measured in the MERCURY 3 trial.[53] This data was mapped to EQ-5D-3L, using an algorithm published in Ara *et al.* (2008)[97], for use in the economic analysis to align with the NICE reference case.[95]
Source of costs	Treatment costs were sourced from the BNF 2023 for all pharmacological interventions.[98]	The literature and databases provide reliable, up-to-date information, that is applicable to the UK clinical practice setting.

	Treatment costs for SLT were sourced from Gazzard *et al.,* 2019.[75] Treatment costs for trabeculectomy were sourced from the NHS national cost collection 2021/22 using the national average cost for very major Glaucoma or Iris Procedures, with CC score 0-1.[99] Administration costs were assumed to be negligible, as all treatments are self-administered. Health state resource use unit costs were sourced from various locations (PSSRU 2022, NHS national cost collection 2021/22, and Violato *et al.,* 2016).[99–101] These unit costs were applied to health state specific resource use values informed by Gazzard *et al.,* 2019a[75], with a multiplier value applied to each health state. A UK clinical expert agreed that the multipliers used and hence, the resource use in each health state, reflects that the ideal outcome (a >30% reduction in IOP) should be associated with the smallest resource use.[102] Unit costs were also applied to the occurrence of AEs, with the occurrence of AEs obtained from published literature. Recommended treatment for each AE (as validated by UK clinical experts) was used to estimate the cost per AE. All costs were converted to a 2022 cost year, using the UK NHS cost inflation index (NHSCII).	Inflation conversion ensured the applicability of all costs to the current real-world setting.
Outcomes	• Total costs • Incremental costs • Disaggregated costs • Total QALYs • Incremental QALYs • Disaggregated QALYs • Total LYs • Incremental LYs • Disaggregated LYs • ICERs	Consistent with the final NICE scope and the NICE reference case.
Uncertainty	• Univariate sensitivity analysis • Scenario analysis • Probabilistic sensitivity analysis	Consistent with NICE reference case.

Abbreviations: AE – Adverse event; BNF – British National Formulary; EQ-5D-3L – EuroQol 5 Dimensions 3 Level Version; ICER – Incremental cost-effectiveness ratio; IOP – Intraocular pressure; LY – Life years; NG – NICE guideline; NHS – National Health Service; NHSCII – National Health Service Cost Inflation Index; NICE – National Institute for Health and Care Excellence; PSS – Personal Social Services; PSSRU – Personal Social Services

B.3.2.3 Intervention technology and comparators

The intervention in the analysis is netarsudil/latanoprost 0.02%/0.005% ophthalmic solution (Roclanda) once daily, in line with the marketing authorisation and the final NICE scope.[87] The dose used aligns with that assessed in the MERCURY 3 trial.[53]

All comparators available as FDCs in the final NICE scope for this appraisal are included in this analysis, as per the anticipated positioning of netarsudil-latanoprost. SLT and 'other glaucoma surgery', namely trabeculectomy, have been included as add-on treatments and not direct comparators (see section B.1.3 for further details on the anticipated positioning of netarsudil-latanoprost). The full list of comparators considered in this appraisal are presented in Table 38.

No stopping rule is applied in the economic analysis, as no stopping rule was implemented in the MERCURY 3 trial, nor is one expected to be used in clinical practice, since netarsudil-latanoprost is expected to be used by patients indefinitely.

Table 38: Comparators included in the economic model

Treatment class (listed in final NICE scope)	Comparator name	Method of inclusion in the model
PGA + BB	Bimatoprost-timolol	Direct comparator
	Latanoprost-timolol	Direct comparator
	Tafluprost-timolol	Direct comparator
	Travoprost-timolol	Direct comparator
CAI + BB	Dorzolamide-timolol	Direct comparator
	Brinzolamide-timolol	Direct comparator
SYMP + BB	Brimonidine-timolol	Direct comparator
CAI + SYMP	Brinzolamide-brimonidine	Direct comparator
SLT	SLT	Add-on treatment
Other glaucoma surgery	Trabeculectomy	Add-on treatment

Abbreviations: BB – Beta blocker; CAI – Carbonic anhydrase inhibitor; NICE – National Institute for Health and Care Excellence; PGA – Prostaglandin analogue; SLT – Selective laser trabeculoplasty; SYMP - Sympathomimetic

B.3.3 Clinical parameters and variables

The evidence base for netarsudil-latanoprost and bimatoprost-timolol is based on the MERCURY 3 trial, which is used to model the clinical effectiveness, safety, and tolerability of these interventions.[53] Given the absence of head-to-head data directly comparing netarsudil-latanoprost to the remaining FDC comparators, an ITC was performed to estimate comparative efficacy through estimates of relative treatment effect, as described in section interventions. Given the absence of head-to-head data directly comparing netarsudil-latanoprost to the remaining FDC comparators, an ITC was performed to estimate comparative efficacy through estimates of relative treatment effect, as described in section B.2.9.

B.3.3.1 Baseline characteristics

As per section B.2.3.2, patient demographics at baseline from the MERCURY 3 trial were used to inform the characteristics of the population entering the model. Table 39 displays the

baseline characteristics of patients entering the model. The mean age of randomised patients forming the ITT population was 67.2 years old, with a 48.1% proportion of males.[53] As described in B.3.2.2, the lifetime time horizon in the model interacts with this baseline age, assuming patients die at 100 years old, and creating a maximum time spent in the model of 32.8 (33) years.

Table 39: Baseline characteristics of patients entering the model

Characteristic	Value	Reference
Age (years) – mean (SD)	67.2 (11.65)	MERCURY 3 CSR[53]
Male – n (%)	207 (48.1)	MERCURY 3 CSR[53]

Abbreviations: CSR – Clinical study report; SD – Standard deviation

B.3.3.2 Transition probabilities

Transition probabilities for patients treated with netarsudil-latanoprost or bimatoprost-timolol moving between IOP based health states were derived from a patient-level data analysis from the MERCURY 3 trial.[53] The choice of thresholds applied in the model were validated with a UK clinical expert, who confirmed their clinical relevance for predicting disease progression in POAG and OHT.[90]

As described in section B.3.2.2, all patients enter the model in the "IOP reduction from baseline <20%" health state. Transition probabilities for netarsudil-latanoprost and bimatoprost-timolol for the first three cycles of the model were derived through patient-level data from MERCURY 3. Patients' change in IOP from baseline (visit 3) was observed at visits 4, 5, and 6, and used to determine health state occupation for each patient at each time point. Probabilities were based only on patients who had data for all four visits (visit 3 [baseline], visit 4, visit 5, and visit 6). The number of patients transitioning from one state to either of the other health states (or remaining within their current health state) was determined for each cycle. These patient counts were then used to derive transition probabilities between health states by dividing the number of patients moving from one health state to another (or remaining in the same state), by the total number of patients transitioning from that state at that time point. The resulting transition probabilities for netarsudil-latanoprost and bimatoprost-timolol for cycles 1-3 are presented in Table 40 and Table 41, respectively.

Table 40: Netarsudil-latanoprost transition probabilities (% of patients)

Cycle	Health state	<20% reduction in IOP	20% - 30% reduction in IOP	>30% reduction in IOP
Baseline -> Cycle 1	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 1 -> Cycle 2	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 2 -> Cycle 3	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – Intraocular pressure

Table 41: Bimatoprost-timolol transition probabilities (% of patients)

Cycle	Health state	<20% reduction in IOP	20% - 30% reduction in IOP	>30% reduction in IOP
Baseline -> Cycle 1	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 1 -> Cycle 2	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 2 -> Cycle 3	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – Intraocular pressure

As stated in section B.2.9, an STC and MAIC were conducted to inform comparative efficacy inputs, given the absence of clinical trials directly comparing netarsudil-latanoprost and other FDC comparators (apart from bimatoprost-timolol). For each comparator, the absolute mean difference between the IOP percentage reduction of netarsudil-latanoprost and the weighted outcomes for each comparator were calculated. These were applied to the transitions for netarsudil-latanoprost in the MERCURY 3 data, creating a new set of transitions across the three IOP health states for each comparator. The comparator absolute mean differences produced by the STC and MAIC are listed in Table 42 and Table 43, respectively. The STC and MAIC produced two sets of results, depending on the time point of data in each of the trials, to maximise the data input whilst managing for heterogeneity in reporting. The time points listed refer to the time points by which data from the ODLASER, MERCURY 3, and Kozobolis trials were taken, respectively. Colour coding specifies which datapoints were used for the baseline analysis. The white cells indicate the data used in the base case, whilst the grey cells indicate data not used in the base case. As the IOP results were only reported at week 8 for the ODLASER trial, the week 8 time point was used for the baseline analysis of brimonidine-timolol. The remaining trials reported results at week 12, as such the week 12 time point was selected for analysis of the other comparators.

These absolute mean differences were applied to the IPD which informed the transitions for netarsudil-latanoprost from the MERCURY 3 data, increasing/decreasing the percentage reduction in IOP by a fixed amount for each patient and time point for the comparators. Table 44 and Table 45 demonstrate the transformed transitions for brimonidine-timolol using the STC and MAIC output, respectively. The transformed transitions for the remaining comparators are presented in Appendix J.

Table 42: STC output - comparator absolute mean differences

Time point*	Week 8, 12, and 12		Week 8, 8, and 8	
Comparator	**Treatment effect of percentage change in IOP**	**SE of treatment effect**	**Treatment effect of percentage change in IOP**	**SE of treatment effect**
Dorzolamide-timolol	[redacted]	[redacted]	[redacted]	[redacted]
Brimonidine-timolol	N/A	N/A	[redacted]	[redacted]
Brinzolamide-brimonidine	[redacted]	[redacted]	[redacted]	[redacted]

Note: White cells maximise the evidence input whilst managing for heterogeneity in reporting. Grey cells specify which data were not used in the base case.
*This row specifies from what time point, besides baseline, data from ODLASER, MERCURY 3, and Kozobolis were taken, respectively.
Source: Netarsudil-latanoprost data were taken from MERCURY 3;[53] brimonidine-timolol data were taken from ODLASER;[61] dorzolamide-timolol and brinzolamide-brimonidine data were taken from Kozobolis.[62]
Abbreviations: IOP – Intraocular pressure; N/A – Not available; SE – Standard error; STC – Simulated treatment comparison

Table 43: MAIC output - comparator absolute mean differences

Time point*	Week 8, 12, and 12		Week 8, 8, and 8	
Comparator	**Treatment effect of percentage change in IOP**	**SE of treatment effect**	**Treatment effect of percentage change in IOP**	**SE of treatment effect**
Dorzolamide-timolol	[redacted]	[redacted]	[redacted]	[redacted]
Brimonidine-timolol	N/A	N/A	[redacted]	[redacted]
Brinzolamide-brimonidine	[redacted]	[redacted]	[redacted]	[redacted]

Note: White cells maximise the evidence input whilst managing for heterogeneity in reporting. Grey cells specify which data were not used in the base case.
*This row specifies from what time point, besides baseline, data from ODLASER, MERCURY 3, and Kozobolis were taken, respectively.
Source: Netarsudil-latanoprost data were taken from MERCURY 3;[53] brimonidine-timolol data were taken from ODLASER;[61] dorzolamide-timolol and and brinzolamide-brimonidine data were taken from Kozobolis.[62]
Abbreviations: IOP – Intraocular pressure; MAIC – Matching-adjusted indirect comparison; N/A – Not available; SE – Standard error

Table 44: Brimonidine-timolol transition probabilities using STC base case output (% of patients)

Cycle	Health state	<20% reduction in IOP	20% - 30% reduction in IOP	>30% reduction in IOP
Baseline -> Cycle 1	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 1 -> Cycle 2	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 2 -> Cycle 3	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – Intraocular pressure; STC – Simulated treatment comparison

Table 45: Brimonidine-timolol transition probabilities using MAIC base case output (% of patients)

Cycle	Health state	<20% reduction in IOP	20% - 30% reduction in IOP	>30% reduction in IOP
Baseline -> Cycle 1	<20% reduction in IOP	[redacted]	[redacted]	[redacted]

	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 1 -> Cycle 2	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 2 -> Cycle 3	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – Intraocular pressure; MAIC – Matching-adjusted indirect comparison

Results for the sensitivity analyses including removing OHT patients from the MERCURY 3 data and removing the 8am data from the three trials are reported in section B.3.10.3.

For interventions not included in the MERCURY 3 trial or the ITC, efficacy was assumed to be equivalent to a drug from the ITC within the same treatment class. Under this assumption, the efficacy of brinzolamide-timolol was assumed to be equivalent to dorzolamide-timolol, and the following comparators were assumed to have the same treatment efficacy as bimatoprost-timolol: latanoprost-timolol, tafluprost-timolol and travoprost-timolol. This is an appropriate assumption to make in the absence of comparative data, since published literature has shown that the efficacy of FDC therapies within the same treatment class is very similar.[103,104]

To model the long-term effects of treatment, data was extrapolated beyond the duration of the MERCURY 3 trial. The model has the functionality for three extrapolation types beyond the trial data for the time horizon. LOCF applies the cycle 2-3 matrices for all remaining cycles (i.e., assumes that patient improvement/worsening post-cycle 3 continues the trajectory observed in cycle 3); 'Final' assumes all patients remain in the health state they are in as cycle 3 is reached (i.e., assumes that patient improvement/worsening remains static after cycle 3); 'Average' applies a mean average of the baseline-cycle 3 values to all remaining cycles (i.e., assumes that patient improvement/worsening post-cycle 3 follows the same trend observed in cycles 1 to 3). The ‘Average’ method was selected for the base case to be reflective of clinical expectations. This extrapolation approach was validated by a UK clinical expert.[105]

B.3.3.3 AEs

AEs of any severity that occurred in ≥5% of patients in the netarsudil-latanoprost arm of the MERCURY 3 trial or in any of the relevant arms of the comparator trials were included in the analysis. While it is standard modelling practice to include severe AEs (AEs of grade 3+) observed in ≥5% patients, following this rule would result in no AEs observed in the MERCURY 3 trial being included in the model, as none met this threshold.[53] AEs are an important factor to capture within the model as they can impact costs (through their management), and QoL (captured as a disutility). The same rule was applied to comparator trials, with AEs of any severity occurring in ≥5% patients in any comparator trials being included in the analysis. A ≥5% incidence cut-off was selected, as the incidence of ocular TEAEs occurring in ≥5% of patients (by maximum severity) was one of the safety outcomes reported in MERCURY 3.[53]

Adverse event probabilities were sourced from the MERCURY 3 trial where possible, and otherwise using literature or similar drug class comparators as proxy values. The probabilities have been converted to monthly rates using a Taylor expansion, as detailed in the equation below:

$$1 - e^{-\frac{-LN(1-AE\ cumalitive\ probability)}{(end\ month-start\ month)}}$$

The resulting AEs and their probability per cycle are presented in Table 46.The per cycle rate of occurrence, for all cycles, was calculated using a Taylor conversion appropriate for the trial follow-up length (see equation above). It is assumed in the model that the AE probability per cycle remains constant throughout the time horizon, which is a conservative assumption in the absence of long-term safety data.

AEs in the model were applied for the duration for which they occurred on average in the MERCURY 3 trial. All severity levels (mild, moderate, and severe) of AEs were included to ensure data were available for all AEs in the model. If AEs did not occur in the trial (abnormal vision, conjunctival bleeding, eyelash discolouration) it was assumed, conservatively, that the AEs were one cycle long. If an AE's end date was not supplied, a value of 120 days was applied, translating to application in all cycles (cycle 4+/treatment duration). AE durations from MERCURY 3 were rounded to the nearest cycle length for use in the model (nearest 30 days).

It was assumed that the duration of AEs in the MERCURY 3 trial (across both arms) is equivalent to the expected AE duration for all comparators. It was also assumed that 'visual impairment' is the same as 'visual disturbance', 'growth of eyelashes' is equivalent to 'change of eyelashes', and 'ocular itching' and 'ocular discomfort' are the same.

The MERCURY 3-sourced duration and comparator-specific probability of each AE was multiplied to create a cost per cycle for cycle 1, cycle 2, cycle 3, and cycle 4+ for each intervention. The total cost per cycle for each AE was totalled for each cycle and intervention, and applied to the number of patients in each respective cycle.

Table 46: Adverse events included in the model and associated probability per cycle

	Netarsudil-latanoprost	Brinzolamide-timolol	Dorzolamide-timolol	Latanoprost-timolol	Tafluprost-timolol	Bimatoprost-timolol	Brimonidine-timolol	Travoprost-timolol	Brinzolamide-brimonidine
Conjunctival hyperaemia	[redacted]	0.00	0.04	0.00	0.01	[redacted]	0.02	0.00	0.02
Cornea verticillata	[redacted]	[redacted]	0.00	[redacted]	[redacted]	[redacted]	0.00	[redacted]	0.00
Conjunctival haemorrhage	[redacted]	[redacted]	0.01	0.00	0.00	[redacted]	0.01	0.00	0.01
Eye pruritis	[redacted]	0.00	0.00	0.00	0.00	[redacted]	0.01	0.00	0.01
Punctate keratitis	[redacted]	0.00	0.01	0.00	0.00	[redacted]	0.02	0.01	0.01
Conjunctivitis allergic	[redacted]	0.00	0.00	0.00	0.00	[redacted]	0.00	0.00	0.01
Viral URTI	[redacted]	0.02	0.02	0.00	[redacted]	[redacted]	0.02	[redacted]	0.02
Hypertension	[redacted]	[redacted]	0.03	[redacted]	0.00	[redacted]	0.02	0.00	0.00
Abnormal vision	[redacted]	[redacted]	0.00	0.00	0.00	[redacted]	0.02	[redacted]	0.02
Blurred vision	[redacted]	0.02	0.02	[redacted]	0.02	[redacted]	0.02	0.02	0.02
Change of eyelashes	[redacted]	0.00	0.00	0.00	0.02	[redacted]	0.00	0.00	0.00
Conjunctival blanching	[redacted]	[redacted]	0.00	[redacted]	[redacted]	[redacted]	0.02	0.00	0.02
Dry eye	[redacted]	0.00	0.01	0.02	0.00	[redacted]	0.01	0.02	0.00
Eye allergy	[redacted]	[redacted]	0.00	0.00	0.00	[redacted]	0.02	0.00	0.02
Eye irritation	[redacted]	0.02	0.00	0.01	0.02	[redacted]	0.01	0.02	0.01
Eye pain	[redacted]	0.02	0.00	0.02	0.02	[redacted]	0.02	0.02	0.02
Eyelash discolouration	[redacted]	[redacted]	0.00	[redacted]	0.02	[redacted]	0.00	[redacted]	0.00
Foreign body sensation in eyes	[redacted]	0.00	0.01	0.02	0.02	[redacted]	0.01	0.00	0.00
Headache	[redacted]	[redacted]	0.02	0.00	0.03	[redacted]	0.02	0.00	0.00
Ocular discomfort	[redacted]	[redacted]	0.02	0.02	0.00	[redacted]	0.02	0.02	0.02
Ocular hyperaemia	[redacted]	0.00	0.00	0.23	0.02	[redacted]	0.00	0.23	0.02
Photophobia	[redacted]	0.00	0.00	0.00	0.02	[redacted]	0.00	0.00	0.00

Visual disturbance	[redacted]	[redacted]	0.00	0.02	0.02	[redacted]	0.00	0.02	0.00
Source	MERCURY 3 CSR[53]	Syed *et al.,* 2011[106]; EMC, 2022[107]	EMC, 2022[107]	Higginbotham *et al.*, 2002[108]; EMC, 2022[107]	Bourne *et al.,* 2019[109]; EMC, 2022[107]	MERCURY 3 CSR[53]	EMC, 2022[107]	Nakano *et al.,* 2015[110]; EMC, 2022[107]	Aoki *et al.,* 2022[111]; EMC, 2022[107]

Abbreviations: CSR – Clinical study report; EMC – Electronic Medicines Compendium; URTI – Upper respiratory tract infection

B.3.3.4 Treatment discontinuation

Discontinuation rates for netarsudil-latanoprost and bimatoprost-timolol were sourced from the MERCURY 3 trial.[53] Discontinuation rates for the remaining comparators were assumed equivalent to bimatoprost-timolol in the absence of data. A scenario analysis is performed where these are assumed equivalent to netarsudil-latanoprost instead (see section B.3.10.3). The number of patients discontinuing in the trial period was translated to a proportion dependent on the total number of patients, before dividing by the number of cycles in the trial and converting to a rate for the treatment arms separately. As a constant rate per cycle was applied, parametric distributions and extrapolations were not required. Table 47 details the rates and sources for each comparator.

When patients discontinue treatment in the model, they are removed from the model health states; discontinued patients do not incur costs or QALYs. This is reflective of clinical practice where discontinued patients will no longer accumulate costs and QoL benefits associated with treatment.

The MERCURY 3 trial[53] and the model from NICE NG81[39] included no formal measure of compliance, noting that no commercially available method was available for direct, single-container monitoring of treatment adherence with multi-dose ophthalmic products. Compliance in the model is therefore assumed to be 100%, with persistence accounting for discontinuation within the trial. Scenario analyses are performed to test the impact of compliance on model results (see section B.3.10.3).

Table 47: Persistence rates

Intervention / comparator	Rate per cycle	Source
Netarsudil-latanoprost	[redacted]	MERCURY 3 CSR[53]
Brinzolamide-timolol	[redacted]	Assumed equivalent to bimatoprost-timolol in the absence of data
Dorzolamide-timolol	[redacted]	Assumed equivalent to bimatoprost-timolol in the absence of data
Latanoprost-timolol	[redacted]	Assumed equivalent to bimatoprost-timolol in the absence of data
Tafluprost-timolol	[redacted]	Assumed equivalent to bimatoprost-timolol in the absence of data
Bimatoprost-timolol	[redacted]	MERCURY 3 CSR[53]
Brimonidine-timolol	[redacted]	Assumed equivalent to bimatoprost-timolol in the absence of data
Travoprost-timolol	[redacted]	Assumed equivalent to bimatoprost-timolol in the absence of data
Brinzolamide-brimonidine	[redacted]	Assumed equivalent to bimatoprost-timolol in the absence of data

Abbreviations: CSR – Clinical study report

B.3.3.5 Mortality

POAG and OHT are not expected to have a direct impact on the life expectancy of patients with these conditions. As such, only general population mortality is applied to the model cohort, sourced from the Office for National Statistics.[112] This methodology is in line with the NG81 cost-effectiveness model in which individuals had a probability of dying which was age-dependent and independent from the stage of OHT or COAG.[39] This approach was also validated by a UK clinical expert.[102]

B.3.4 Measurement and valuation of health effects

B.3.4.1 HRQoL data from clinical trials

HRQoL data was captured in the MERCURY 3 trial using the Short Form-36 (SF-36) questionnaire.[53] This instrument measures eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. SF-36 was measured in individuals in MERCURY 3 at screening and at study completion (month 6).

The SF-36 physical component (aggregate) scores, which provide a summary of the granular recordings, from the MERCURY 3 trial show that the mean scores were broadly comparable between the treatment groups in the aggregate physical component score, with no statistical differences between the treatment arms (see section B.2.6.8). This is indicative of the SF-36 subscales, where little difference between the two arms was observed. Over the trial period, the values in the netarsudil-latanoprost arm marginally improved, whilst a marginal worsening was observed in the bimatoprost-timolol arm. Overall, patients in either treatment arm had similar perceptions of their general health at the different time points.

B.3.4.2 Mapping

SF-36 data for all eight scales across both treatment arms from the MERCURY 3 trial was mapped to EQ-5D-3L, to align with the NICE reference case.[95] The EQ-5D-3L data was applied for the three health states in the in the model across all treatment arms.

Published literature was reviewed to identify the most appropriate algorithm to use to map SF-36 to EQ-5D for the POAG and OHT population. Four algorithms (Ara and Brazier (2008)[97], Kim *et al*. (2014)[113], Maund *et al.* (2012)[114] and Rowen *et al*. (2009)[115]) were identified in the literature to map SF-36 to EQ-5D, and each of these were reviewed for their appropriateness, based on the applicable disease area, the models used, the number of observations, and the countries included. None of the algorithms identified were developed for eye-related conditions only. Two of the identified algorithms, Ara and Brazier (2008)[97], and Rowen *et al.* (2009)[115] were considered appropriate for mapping SF-36 data from MERCURY 3 CSR[53] for this analysis, as these algorithms were developed using datasets collected in the UK and included patient observations with various indications.

The Ara and Brazier (2008)[97] method was selected for the base case, due to its alignment with existing utility values in the literature. The Rowen (2009)[115] mapping algorithm has been explored as a scenario analysis (see section B.3.10.3). An equivalent regression method (Brazier and Roberts 2004) as Ara and Brazier (2008) had previously been utilised for mapping SF-36 data to EQ-5D as published in NICE HST5.[116,117]

The methodology employed to perform the mapping analysis can be found in Appendix M.

B.3.4.3 HRQoL studies

An SLR was conducted in November 2022 to identify studies reporting HRQoL of patients with POAG and OHT. Full details of the methodology and results of included studies are presented in Appendix H.

All three of the studies identified from the review described utility values elicited from the same RCT, the LiGHT study; Gazzard 2019a[75], Gazzard 2019b[88], and Gazzard 2022[118]. All three of the publications contained utility scores, all of which were valued using EQ-5D-5L, amongst other valuation tools.

The health state definitions in two of the identified studies (Gazzard 2019a[75] and Gazzard 2019b[88]) were based on severity of glaucoma (as described in section B.3.1) and therefore did not align with the health states used in this analysis. As such, the health state utility values (HSUVs) from these studies were not suitable for use in this analysis. The third identified study, Gazzard 2022[118], reported utility scores from baseline to 72 months in 6-month intervals for both treatment arms (eye drops and SLT). However, these utility values were for the entire treatment group and were not reflective of health states, therefore were not appropriate for use in this analysis.

Since quality-of-life data obtained from the SLR was not appropriate for the model health states in this appraisal, HSUVs were estimated using data from the MERCURY 3 trial only.

B.3.4.4 Adverse reactions

As detailed in section B.3.3.3, AEs of any severity that occurred in ≥5% patients in the netarsudil-latanoprost arm of the MERCURY 3 trial or in any of the relevant arms of the comparator trials were included in the analysis. Since the SLR did not provide any utility decrements associated with the relevant AEs, targeted searches were undertaken to source these values for each AE. In instances where values for a particular AE could not be found, the values associated with a similar AE were applied.

Utilities for each AE were applied in the model for their average duration in the MERCURY 3 trial. AE durations sourced from the MERCURY 3 trial included all severity levels to ensure data were available for all AEs of interest. If AEs did not occur in the trial (abnormal vision, conjunctival bleeding, eyelash discolouration) it was assumed conservatively, that the AEs were one cycle long. If an AE end date was not supplied, a value of 120 days was applied, translating to application in all cycles (cycle 4+/treatment duration). AE durations were rounded to the nearest cycle length in the model (nearest 30 days).

The majority of the AE utility decrement values were sourced from Sullivan *et al*. 2011;[119] this source was selected since it is a catalogue of EQ-5D index scores (NICE's preferred method of HRQoL measurement) for a range of conditions based on UK preferences, therefore aligning with the context of this appraisal. All utility decrement values and sources are listed in Table 48, which have been validated by a UK clinical expert.

Table 48: Disutility due to AEs

AE	Disutility decrement	Source
Conjunctival hyperaemia	0.0003	Sullivan *et al.* 2011[119]
Cornea verticillata	0.0000	Wesberry *et al.* 2022[120]
Conjunctival haemorrhage	0.0003	Sullivan *et al.* 2011[119]
Eye pruritis	0.0480	Sullivan *et al.* 2011[119]
Punctate keratitis	0.0408	Sullivan *et al.* 2011[119]; MSD Manual Consumer Version, 2022[121]
Conjunctivitis allergic	0.0003	Sullivan *et al.* 2011[119]
Viral URTI	0.2000	NICE 2021 (TA699)[122]
Hypertension	0.133	NICE 2018 (TA498)[123]
Abnormal vision	0.0642	Sullivan *et al.* 2011[119]
Blurred vision	0.0642	Sullivan *et al.* 2011[119]
Change of eyelashes	0	-
Conjunctival blanching	0.0003	Sullivan *et al.* 2011[119]
Dry eye	0.113	Nordmann *et al.* 2003[124]
Eye allergy	0.0092	Sullivan *et al.* 2011[119]
Eye irritation	0.0092	Sullivan *et al.* 2011[119]

Eye pain	0.0092	Sullivan *et al.* 2011[119]
Eyelash discolouration	0	-
Foreign body sensation in eyes	0	-
Headache	0.0266	Sullivan *et al.* 2011[119]
Ocular discomfort	0.0092	Sullivan *et al.* 2011[119]
Ocular hyperaemia	0.0092	Sullivan *et al.* 2011[119]
Photophobia	0.01	SMC 2020 (SMC2261)[125]
Visual disturbance	0.0408	Sullivan *et al.* 2011[119]

Abbreviations: AE – Adverse event; SMC – Scottish Medicines Consortium; TA – Technology appraisal; URTI – Urinary tract infection

B.3.4.5 HRQoL data used in the CEA

A mapping exercise was conducted to generate EQ-5D-3L HSUVs for inclusion in the economic model, as described in section B.3.4.2. Data from all patients enrolled in MERCURY 3 at both time points (visit 1 [Screening] and visit 9 [Month 6]) were used to generate mean utility values. Patients were grouped into health states at each time point according to their reduction in IOP from baseline. As visit 9 IOP data were not available, the closest available time point was used (visit 6 [Month 3]). Utility values used for the health states in the model base-case and scenario analyses are presented in Table 49 and Table 50, respectively.

The Ara and Brazier (2008)[97] method was selected for the base case, due to its alignment with existing utility values in the literature. The Rowen (2009)[115] mapping algorithm has been explored as a scenario analysis (see section B.3.10.3).

Table 49: HSUVs used in the base case of the economic analysis (Ara and Brazier [2008])

Health state	Utility value (SE)
<20% reduction in IOP	[redacted]
20-30% reduction in IOP	[redacted]
>30% reduction in IOP	[redacted]

Abbreviations: IOP – Intraocular pressure; SE – Standard error

Table 50: HSUVs used in a scenario of the economic analysis (Rowan [2009])

Health state	Utility value (SE)
<20% reduction in IOP	[redacted]
20-30% reduction in IOP	[redacted]
>30% reduction in IOP	[redacted]

Abbreviations: IOP – Intraocular pressure; SE – Standard error

The QoL associated with caregivers was not included in the model, as a UK clinical expert confirmed that patients with POAG or OHT are unlikely to require caregiver support.[102]

B.3.4.5.1 Utility adjustments based on age

As the analysis is conducted over a lifetime time horizon, a general decline in HRQoL with age is expected. A method described in Ara and Brazier (2010) is used in the base case to model the expected decline in HRQoL with age.[126] Utility values are adjusted to account for the natural decline in HRQoL as the cohort ages, using the baseline age and proportion of males in the model which are informed by data from MERCURY 3.[53] The regression model used to estimate this decline is based on EQ-5D data from the Health Survey for England in 2003 and 2006:[127]

$$U_{base}(age, gender) = 0.9508566 + 0.0212126 * Male - 0.0002587 * Age - 0.0000332 * (Age)^2$$

B.3.4.6 Summary of utility values used for cost-effectiveness analysis

Table 51 summarises the utility values used in the economic analysis.

Table 51: Summary of utility values used in the economic analysis

State	Utility value: mean (standard deviation)	95% confidence interval	Reference	Justification
HSUVs				
<20% reduction in IOP	[redacted]	[redacted]	MERCURY 3 CSR [53] and transformation using Ara and Brazier (2008)[97]	Generated from mapping study.
20-30% reduction in IOP	[redacted]	[redacted]	MERCURY 3 CSR [53] and transformation using Ara and Brazier (2008)[97]	
>30% reduction in IOP	[redacted]	[redacted]	MERCURY 3 CSR[53] and transformation using Ara and Brazier (2008)[97]	
Adverse event disutility values				
Conjunctival hyperaemia	0.0003	N/A: Disutility values and AE probabilities are interacted, and summed for each comparator, to calculate to the total disutility for each cycle. This value is varied in the sensitivity analyses.	Sullivan *et al*. 2011[119]	Sourced from published literature.
Cornea verticillata	0.0000		Wesberry *et al*. 2022[120]	
Conjunctival haemorrhage	0.0003		Sullivan *et al*. 2011[119]	
Eye pruritis	0.0480		Sullivan *et al*. 2011[119]	
Punctate keratitis	0.0408		Sullivan *et al*. 2011[119]; MSD Manual Consumer Version, 2022[121]	
Conjunctivitis allergic	0.0003		Sullivan *et al*. 2011[119]	
Viral URTI	0.2000		NICE 2021 (TA699)[122]	
Hypertension	0.133		NICE 2018 (TA498)[123]	
Blurred vision	0.0642	N/A: Disutility values and AE probabilities are interacted, and summed for each comparator, to calculate to the total disutility for each cycle. This value is varied in the sensitivity analyses.	Sullivan *et al*. 2011[119]	Sourced from published literature.
Change of eyelashes	0		Assumed that no disutility is incurred	
Conjunctival blanching	0.0003		Sullivan *et al*. 2011[119]	
Dry eye	0.113		Nordmann *et al*. 2003[124]	
Eye allergy	0.0092		Sullivan *et al*. 2011[119]	
Eye irritation	0.0092		Sullivan *et al*. 2011[119]	
Eye pain	0.0092		Sullivan *et al*. 2011[119]	
Eyelash discolouration	0		Assumed that no disutility is incurred	
Foreign body sensation in eyes	0		Assumed that no disutility is incurred	
Headache	0.0266		Sullivan *et al*. 2011[119]	
Ocular discomfort	0.0092		Sullivan *et al*. 2011[119]	
Ocular hyperaemia	0.0092		Sullivan *et al*. 2011[119]	
Photophobia	0.01		SMC 2020 (SMC2261)[125]	
Visual disturbance	0.0408		Sullivan *et al*. 2011[119]	

Abbreviations: AE – Adverse event; CSR – Clinical study report; IOP – Intraocular pressure; N/A – Not available; SMC – Scottish Medicines Consortium; TA – Technology appraisal; URTI – Urinary tract infection

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted in November 2022 to identify studies reporting cost and healthcare resource use (HCRU) data for patients with POAG or OHT. Full details of the methodology and results are presented in Appendix I.

Cost and HCRU inputs considered in the base case analysis comprise direct medical costs including drug acquisition costs, administration costs, costs associated with the management of AEs, the cost of concomitant treatment with SLT and/or trabeculectomy, and background disease management costs. Costs were sourced from the British National Formulary (BNF) 2023[98], NHS Reference Costs for 2021/22[99], PSSRU 2022[100], and published literature.

B.3.5.1 Intervention and comparators' costs and resource use

The SmPC for each comparator dictated the dose assumed in the model, with midpoints considered where ranges were provided. The cost per dose was calculated using either the drug tariff costs or NHS indicative price (user setting) from the BNF 2023[98], which were converted in the model from cost per pack, to cost per unit, to cost per drop. The cost per drop and recommended dose per month were then interacted for each compactor class. Within class market shares based on historical UK sales data were used to weight comparator costs based on the individual drugs within each class.

Administration costs were assumed to be negligible, as all FDCs considered in the model are self-administered. Compliance in the model is assumed to be 100% for all comparators in line with evidence from published literature, but is varied in scenario analyses to assess the impact on model results.[39,53] Persistence data were used to model discontinuation of treatment and is described in section B.3.3.4.

For the acquisition cost per cycle of netarsudil-latanoprost, the list price (£14.00) and bottle size (2.5 ml) were used to calculate the cost per drop (£0.28) based on a 0.05 ml drop conversion. The cost per drop (£0.28) is multiplied by the frequency per cycle (60.88 drops, i.e., twice a day), and administration costs (£0.00) are added to calculate a total cost per cycle of £17.05.

Table 52 displays the dosing for each FDC considered in the model. Table 53 details the cost per pack for each product within each comparator class. Costs are converted to a cost per drop, for use in later calculations.

The dose, cost per drop, and within class market share for each product were interacted to create a weighted cost per cycle for each treatment class. Table 54 and Table 55 detail the costs and sources for the brinzolamide-timolol comparator, demonstrating the structure applied for the remaining comparators. Table 56 summarises the total cost per cycle for the intervention and comparators.

Table 52: Intervention/comparator dosing

Active ingredient	Product listing in source	Frequency of administration per day	Frequency of administration per model cycle (n)*
Netarsudil-latanoprost	Roclanda	Once daily, per eye	60.88

Active ingredient	Product listing in source	Frequency of administration per day	Frequency of administration per model cycle (n)*
Brinzolamide-timolol	AZARGAEYEDR5/10MG5ML	Twice daily, per eye	121.75
	TIMOLOL/BRINZOLAMIEYEDR5/10MG5ML	Twice daily, per eye	121.75
Dorzolamide-timolol	DORZOLAMID/TIMOLOLEYEDROPS2%60.2ML	Twice daily, per eye (one UD does two eyes)	60.88
	DORZOL/TIMOLOLSDZEYEDROPS5ML	Twice daily, per eye	121.75
	DORZOL/TIMOLOL ZVA EYEDROPS5ML	Twice daily, per eye	121.75
	DORZOLAMID/TIMOLOLEYEDROPS5ML	Twice daily, per eye	121.75
	COSOPTEYEDROPS5ML	Twice daily, per eye	121.75
	COSOPTMSDEYEDROPS5ML	Twice daily, per eye	121.75
	COSOPTEYEDROPU/D60.2ML	Twice daily, per eye (one UD does two eyes)	60.88
	COSOPTIMULTIEYEDROPS10ML	Twice daily, per eye	121.75
	EYLAMDOPFEYEDROPS5ML	Twice daily, per eye	121.75
	VIZIDORDUOPFEYEDROPS5ML	Twice daily, per eye	121.75
Latanoprost-timolol	LATANOPROST/TIMOLEYEDROPS2.5ML	Once daily, per eye	60.88
	LATANOPROST/TIZVAEYEDROPS2.5ML	Once daily, per eye	60.88
	LATANOPRST/TIMSDZEYEDROPS2.5ML	Once daily, per eye	60.88
	FIXAPOSTPFE/DUDV30.2ML	Once daily, per eye (one UD does two eyes)	30.44
	MEDOX50MCG/5MG/ML2.5ML	Once daily, per eye	60.88
	XALACOMEYEDROPS2.5ML	Once daily, per eye	60.88
Tafluprost-timolol	TAPTIQOME/D15Y&5MG30.3ML	Once daily, per eye (one UD does two eyes)	30.44
Bimatoprost-timolol	BIMATOPRO/TIMOZVAEYEDROPS3ML	Once daily, per eye	60.88
	BIMATOPROST/TIMOLOEYEDROPS3ML	Once daily, per eye	60.88
	EYZEETANEYEDROPS3ML	Once daily, per eye	60.88
	GANFORTEYEDROPS33ML	Once daily, per eye	60.88
	GANFORTEYEDROPS3ML	Once daily, per eye	60.88
	GANFORTVIALSU/D30.4ML	Once daily, per eye (one UD does two eyes)	30.44
Travoprost-timolol	TRAVOPROSTTIMOLOLEYE/DROPSOL2.5ML	Once daily, per eye	60.88
	DUOTRAVEYE/DROPSOL2.5ML	Once daily, per eye	60.88
Brinzolamide-brimonidine	Simbrinza 10mg/ml / 2mg/ml eye drops	Twice daily, per eye	121.75
Brimonidine-timolol	COMBIGANEYEDROPS35ML	Twice daily, per eye	121.75
	COMBIGANEYEDROPS5ML	Twice daily, per eye	121.75

*Interacted with cycle length in the model (30.4375)

Abbreviations: mg – Milligram; ml – Millilitre; PI – Prescribing information; UD – Unit dose

Table 53: Intervention/comparator cost per pack

Active ingredient	Product listing in source	NHS indicative price[98]	Drug tariff price[98]	Units per pack	Unit
Netarsudil-latanoprost	-	£14.00		2.50	ml
Brinzolamide-timolol	AZARGAEYEDR5/10MG5ML	11.05	4.04	5.00	ml
	TIMOLOL/BRINZOLAMIEYEDR5/10MG5ML	4.04	4.04	5.00	ml
Dorzolamide-timolol	DORZOLAMID/TIMOLOLEYEDROPS2%60.2ML	28.59	24.13	60.00	unit dose
	DORZOL/TIMOLOLSDZEYEDROPS5ML	2.10	1.73	5.00	ml
	DORZOL/TIMOLOL ZVA EYEDROPS5ML	2.10	1.73	5.00	ml
	DORZOLAMID/TIMOLOLEYEDROPS5ML	2.10	1.73	5.00	ml
	COSOPTEYEDROPS5ML	10.05	1.73	5.00	ml
	COSOPTMSDEYEDROPS5ML	10.05	1.73	5.00	ml
	COSOPTEYEDROPU/D60.2ML	28.59	24.13	60.00	unit dose
	COSOPTIMULTIEYEDROPS10ML	28.00	28.00	10.00	ml
	EYLAMDOPFEYEDROPS5ML	8.13	8.13	5.00	ml
	VIZIDORDUOPFEYEDROPS5ML	8.14	8.13	5.00	ml
Latanoprost-timolol	LATANOPROST/TIMOLEYEDROPS2.5ML	3.33	3.47	2.50	ml
	LATANOPROST/TIZVAEYEDROPS2.5ML	3.33	3.47	2.50	ml
	LATANOPRST/TIMSDZEYEDROPS2.5ML	3.33	3.47	2.50	ml
	FIXAPOSTPFE/DUDV30.2ML	13.49	13.49	30.00	unit dose
	MEDOX50MCG/5MG/ML2.5ML	14.00	3.47	2.50	ml
	XALACOMEYEDROPS2.5ML	14.32	3.47	2.50	ml
Tafluprost-timolol	TAPTIQOME/D15Y&5MG30.3ML	14.50	14.50	30.00	unit dose
Bimatoprost-timolol	BIMATOPRO/TIMOZVAEYEDROPS3ML	14.16	14.16	3.00	ml
	BIMATOPROST/TIMOLOEYEDROPS3ML	14.16	14.16	3.00	ml
	EYZEETANEYEDROPS3ML	14.16	14.16	3.00	ml
	GANFORTEYEDROPS33ML	14.16	14.16	3.00	ml
	GANFORTEYEDROPS3ML	14.16	14.16	3.00	ml
	GANFORTVIALSU/D30.4ML	17.94	17.94	30.00	unit dose
Travoprost-timolol	TRAVOPROSTTIMOLOLEYE/DROPSOL2.5ML	7.88	5.71	2.50	ml
	DUOTRAVEYE/DROPSOL2.5ML	13.95	5.55	2.50	ml
Brinzolamide-brimonidine	Simbrinza 10mg/ml / 2mg/ml eye drops	9.23	9.23	5.00	ml

Active ingredient	Product listing in source	NHS indicative price[98]	Drug tariff price[98]	Units per pack	Unit
Brimonidine-timolol	COMBIGANEYEDROPS35ML	27.00	27.00	5.00	ml
	COMBIGANEYEDROPS5ML	10.00	12.90	5.00	ml

Abbreviations: ml – Millilitre; NHS – National Health Service; UD – Unit dose

Table 54: Brinzolamide-timolol cost calculation (part 1)

Product	Weight (%)	Frequency of administration per cycle	Cost per drop (£)	Acquisition cost per cycle (£)	Weighted average acquisition cost per cycle (£)
Azarga 5ml	36.26 %	122	0.11	13.45	(36.26%*13.45) + (63.74%*4.92) = 8.01
Azarga 5ml PI	63.74 %	122	0.04	4.92	
Source	IQVIA 2023[128]	EMC 2023[129]	BNF 2023[98]		

Abbreviations: BNF – British National Formulary; EMC – Electronic Medicines Compendium; ml – Millilitre; PI – Prescribing information

Table 55: Brinzolamide-timolol cost calculation (part 2)

Product	Weight (%)	Admin cost per cycle (£)	Weighted average admin cost per cycle (£)	Weighted average acquisition cost per cycle (£)	Total cost per cycle (£)
Azarga 5ml	36.26%	0.00	(36.26%*0) + (63.74%*0) = 0.0	8.01	0.0 + 8.01 = 8.01
Azarga 5ml PI	63.74%	0.00			
Source	IQVIA 2023[128]	Assumed 0 per cycle for each product specific, then multiplied by number of cycles		See part 1 table	Totals weighted admin and acquisition cost per cycle

Abbreviations: PI – Prescribing information

Table 56: Intervention and comparator cost per cycle

Intervention/comparator	Total cost per cycle (£)
Netarsudil-latanoprost	17.05
Brinzolamide-timolol	8.01
Travoprost-timolol	12.79
Dorzolamide-timolol	9.94
Latanoprost-timolol	11.37
Tafluprost-timolol	14.71
Bimatoprost-timolol	15.03
Brinzolamide-brimonidine	11.24
Brimonidine-timolol	13.74

B.3.5.2 Health state unit costs and resource use

Table 57 presents the health state costs and resource use. Baseline health state resource use was informed by Gazzard *et al.* 2019a[75], with a multiplier value applied to each health state, based on UK clinical expert input to reflect the increase in resource use required by more severe patients. The <20% IOP reduction health state applied a 5% multiplier, whilst a 2.5% multiplier was used for the 20-30% IOP reduction health state, and a 0% multiplier was applied for the >30% IOP reduction health state.

Health state resource use unit costs were sourced from various locations (PSSRU 2022, NHS England 2021, and Violato *et al.* 2016)[99–101] and validated by UK clinical experts. These unit costs were applied to each resource, and the total cost per cycle for each resource use was summed for each of the three health states.

Table 57: Health state costs and resource use

	Health state costs and resource use				
Resource	**Unit cost (£)**	**Code**	**Health state**	**Resource use per cycle**	**Total cost per cycle (£)**
GP visits	42.00	PSSRU: per surgery cost per consultation cost, including direct care staff costs	<20% reduction in IOP	0.0182	0.76
			20% - 30% reduction in IOP	0.0178	0.75
			>30% reduction in IOP	0.0173	0.73
A&E attendance	143.74	NHS: Total outpatient attendance #18 Emergency Medicine Service	<20% reduction in IOP	0.012	1.64
			20% - 30% reduction in IOP	0.011	1.60
			>30% reduction in IOP	0.010	1.56
Ophthalmologist appointments	141.97	NHS: Total outpatient attendance #130 Ophthalmology Service	<20% reduction in IOP	0.234	33.25
			20% - 30% reduction in IOP	0.229	32.46
			>30% reduction in IOP	0.223	31.67
Optometrist visit	57.54	Violato *et al.* 2016	<20% reduction in IOP	0.234	13.48
			20% - 30% reduction in IOP	0.229	13.16
			>30% reduction in IOP	0.223	12.84
Total	-		<20% reduction in IOP	-	**49.13**
			20% - 30% reduction in IOP	-	**47.96**
			>30% reduction in IOP	-	**46.79**
Source	(Violato *et al.* 2016; PSSRU, 2022; NHS England, 2021)[99–101]		-	Gazzard *et al.* 2019a[75]	-

Abbreviations: A&E – Accident and emergency; IOP – Intraocular pressure; GP – General practitioner; NHS – National Health Service; PSSRU – Personal Social Services Research Unit

B.3.5.3 Adverse reaction unit costs and resource use

For each AE included in the model (those that occurred in ≥5%, as described in section B.3.3.3), the resource use required (e.g., the type and frequency of medical appointment) was informed by UK clinical expert input. The costs for each resource use type were sourced from NHSE, PSSRU and Violato *et al.* 2016.[99–101] The total cost per AE was calculated by multiplying the resource use unit cost by the event frequency. For each treatment, the cost was applied by taking the adverse event total costs and multiplying by the probability of the AE occurring for that therapy.

Table 58 outlines the costs, resource use and sources for managing the AEs included in the model.

Table 58: Adverse event costs and resource use

Adverse event	AE total cost (£)	AE resource use	Source (resource use)	Source (cost)
Conjunctival hyperaemia	212.96	Ophthalmology appointment x1.5	Resource use informed by UK clinical expert input	NHS Cost Collection, 2023[99]
Cornea verticillata	141.97	Ophthalmology appointment x1		NHS Cost Collection, 2023[99]
Conjunctival haemorrhage	283.95	Ophthalmology appointment x2		NHS Cost Collection, 2023[99]
Eye pruritis	441.41	Ophthalmology appointment x1.5 and dermatology appointment x1.5		NHS Cost Collection, 2023[99]
Punctate keratitis	354.93	Ophthalmology appointment x2.5		NHS Cost Collection, 2023[99]
Conjunctivitis allergic	283.95	Ophthalmology appointment x2		NHS Cost Collection, 2023[99]
Viral URTI	42.00	GP appointment x1		PSSRU, 2022[100]
Hypertension	537.86	NHS England, 2021 listed cost		NHS Cost Collection, 2023[99]
Abnormal vision	283.95	Ophthalmology appointment x2		NHS Cost Collection, 2023[99]
Blurred vision	283.95	Ophthalmology appointment x2		NHS Cost Collection, 2023[99]
Change of eyelashes	0.00	No treatment required		UK clinical expert validation
Conjunctival blanching	0.00	No treatment required		UK clinical expert validation
Dry eye	0.69	Hypromellose eye drops x1 (1-2 drops three times per day as needed)		BNF 2023[98]
Eye allergy	283.95	Ophthalmology appointment x2		NHS Cost Collection, 2023[99]
Eye irritation	0.69	Hypromellose eye drops x1 (1-2 drops three times per day as needed)		BNF 2023[98]
Eye pain	283.95	Ophthalmology appointment x2		NHS Cost Collection, 2023[99]
Eyelash discolouration	0.00	No treatment required		UK clinical expert validation
Foreign body sensation in eyes	283.95	Ophthalmology appointment x2		NHS Cost Collection, 2023[99]
Headache	2.44	Paracetamol x1 (1-2 tablets up to four times a day)		BNF 2023[98]
Ocular discomfort	283.95	Ophthalmology appointment x2		NHS Cost Collection, 2023[99]
Ocular hyperaemia	0.00	No treatment required		UK clinical expert validation
Photophobia	283.95	Ophthalmology appointment x2		NHS Cost Collection, 2023[99]
Visual disturbance	283.95	Ophthalmology appointment x2		NHS Cost Collection, 2023[99]

Abbreviations: AE – Adverse event; BNF – British National Formulary; GP – General practitioner; N/A – Not applicable; NHS – National Health Service; UK – United Kingdom; URTI – Urinary tract infection

B.3.5.4 Miscellaneous unit costs and resource use

The cost of two concomitant treatments (SLT and/or trabeculectomy) are included in the model, by applying a proportion specific to each health state. Unit costs for each procedure are interacted with the per cycle probability that a patient undergoes the procedure in each health state, to calculate an average per cycle cost for each health state. These values are applied in every cycle for every patient, relative to their health state. Table 59 outlines the cost inputs for these concomitant treatments.

The unit costs for SLT and trabeculectomy were sourced from Gazzard *et al.* 2019a[75] and NHS National Cost Collection, 2021[99], respectively. The proportion of patients undergoing each of the procedures was sourced from secondary care data for 2018-2022, Hospital Episode Statistics (HES; NHS digital) and validated by a UK clinical expert.[130] The average proportion of patients expected to receive each treatment was estimated for years 1-5 in the budget impact model, by applying the average annual change in patients over the 2018-2022 data to the most recent value (2022). In the SLT calculation, patient data were split into inpatients and outpatients, with annual rates for each and a pooling for a single overall value.

The average proportion of patients estimated to receive each treatment in year 1 was applied to the baseline health state (<20% reduction in IOP), with the assumption that the following health states involved a 10% multiplier decrement, under the expectation that the proportion of patients eligible for the procedures will decrease as reduction in IOP improves. The values applied in the model, which were validated by a UK clinical expert, are detailed in Table 59.[102]

A UK clinical expert validated that it is unlikely that patients with POAG or OHT would require caregiver support: therefore, caregiver costs are not included in the model.

Table 59: Summary of miscellaneous (concomitant) costs used in the economic analysis

Health state	SLT cost per cycle (£)	Trabeculectomy cost per cycle (£)
<20% reduction in IOP	0.67	42.01
20% - 30% reduction in IOP	0.61	38.19
>30% reduction in IOP	0.56	35.01
Unit cost (£)	167.10	2609.96
Unit cost source	Gazzard *et al.* 2019[75]	NHS National Cost Collection, 2021[99]
Proportion of patients eligible for treatment by health state (<20%, 20% - 30%, >30% reduction in IOP) (%)	0.40, 0.36, 0.33	1.61, 1.46, 1.34

Abbreviations: IOP – Intraocular pressure; NHS – National Health Service; SLT – Selective laser trabeculoplasty

B.3.6 Severity

Treatment for POAG or OHT is not expected to extend the length of life for patients with these conditions. Furthermore, there are no additional factors that are missing from the quality-adjusted life year (QALY) calculations. Therefore, a decision modifier is not included in this appraisal.

B.3.7 Uncertainty

Uncertainty in the model was generally managed using several sensitivity analyses, detailed in section B.3.10.

The principal areas of uncertainty in the analysis and the management approach are detailed in Table 60.

Table 60: Areas of uncertainty and management

Area of uncertainty	Approach to management
Efficacy	
Comparator efficacy: the primary clinical data source for this appraisal (MERCURY 3) includes head-to-head data for netarsudil-latanoprost and bimatoprost-timolol only.	Comparative efficacy data was generated using data from an unanchored MAIC and STC methodologies (STC was preferred in the base case). In addition to MERCURY 3, comparative efficacy data for the economic model was generated based on efficacy data sourced from an SLR for three further comparators: brimonidine-timolol, brinzolamide-brimonidine and dorzolamide-timolol. For the four remaining comparators, for which comparative efficacy could not be generated, efficacy in the economic model was assumed equal to bimatoprost-timolol, since all four comparators are within the same treatment class (PGA+BB) as bimatoprost-timolol. Assuming equivalent efficacy in the PGA+BB and CAI + BB classes is supported by published literature.[104] The approach may incur biases for the following reasons: • The limitations of the unanchored MAIC and STC analyses are detailed in section B.2.9.2.5 and section B.2.9.3.5, which may ultimately affect the credibility of the comparative efficacy data generated. For instance, failing to account for all clinically important treatment effect modifiers and prognostic factors. • The assumption of equivalent efficacy within the PGA+BB and CAI + BB classes for the outstanding comparators may be an under- or over-estimate the efficacy of some of the comparators.
Long-term efficacy: efficacy data for the technology and most comparators are available for between 3-6 months of follow-up only.	Extrapolations (discussed in section B.3.3.2) are applied after the last time point for which data is available (cycle 3 in the model), using multiple methods (LOCF, final, average) to account for the validity of assumptions and uncertainty in the long-term. The assumptions applied for each extrapolation method are detailed in section B.3.3.2. The base case uses the average approach. The other two approaches are tested as scenario analyses to explore uncertainty around the estimates.
Persistence data: only available for netarsudil-latanoprost and bimatoprost-timolol.	Persistence data were not readily available for comparators outside the MERCURY 3 trial; for these comparators, persistence was assumed equivalent to bimatoprost-timolol in the absence of data. A scenario analysis is included where persistence is set equal to the netarsudil-latanoprost arm.
Compliance data: no data available for the intervention or comparators.	A UK clinical expert indicated that treatment compliance ideally should be 100%, but the reality is that this is not always the case despite studies assuming so.[102] However, in the absence of published data, compliance for all comparators and the intervention was assumed to be 100% in the base case. A scenario analysis has been included to test the impact of reducing compliance.
AEs	

AE probability data: lack of direct and consistent AE data from comparator trials.	AE rates for most comparators were sourced from European Medicines Agency (EMA) SmPCs and other published literature where available, with proxies for AE rates used where data were unavailable. It is assumed that SmPC AE rates are equivalent to rates reported in studies and reported for 3-month periods. See section B.3.3.3 for more information.
Duration of AEs: lack of data on duration of AEs for comparators.	AE duration was assumed equal for all comparators, based on MERCURY 3 data for netarsudil-latanoprost and bimatoprost-timolol arms, including AEs of all severities.
QoL	
QoL data: only SF-36 data were reported in the MERCURY 3 trial.	A mapping of SF-36 to EQ-5D was conducted, using a conversion method detailed in Ara and Brazier 2008.[97] This method may incur the following issues: • The mapping algorithm used was developed in a patient group consisting of 6,350 patients in the UK with a range of health conditions, and was not specific to patients suffering from glaucoma.[97] However, Ara and Brazier 2008 was considered to be a more appropriate method than Rowen 2009,[115] which was only conducted using inpatients or outpatients at hospital. • The model was assessed for its accuracy in predicting mean EQ-5D utilities from the mean SF-36 scores in the absence of PLD. As trial PLD was available from MERCURY 3, this is considered to be a limitation of the algorithm.
Caregiver costs and QoL: not included in the model.	The impact of caregivers is considered negligible for patients with POAG or OHT; this was validated by a UK clinical expert and hence, is not included in the model.[102] However, in reality, some patients with POAG/OHT may require caregiver support, such as those with arthritic conditions needing assistance to apply eye drops.

Abbreviations: AE – Adverse event; BB – Beta blocker; BNF – British National Formulary; COAG – Chronic open-angle glaucoma; EMA – European Medicines Agency; IOP – Intraocular pressure; ITT – Intention-to-treat; LOCF – Last observation carried forward; MAIC – Matching-adjusted indirect comparison; ml – Millilitre; NG81 – NICE Guideline 81; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; OHT – Ocular hypertension; PGA – Prostaglandin analogue; PLD – patient-level data; POAG – Primary open-angle glaucoma; QoL – Quality-of-life; SF-36 – Short Form-36; SLT – Selective laser trabeculoplasty; SmPC – Summary of Product Characteristics; STC – Simulated treatment comparison; UK – United Kingdom

B.3.8 Summary of base case analysis inputs and assumptions

B.3.8.1 Summary of base-case analysis inputs

A summary of the base case analysis inputs is presented in Table 61.

Table 61: Summary of variables applied in the base-case economic analysis

Variable	Value	OWSA			Within PSA varied by	Reference to section in submission
		SE	Lower bound	Upper bound		
Model settings						
Cohort size	1,000	-	-	-	-	-
Time horizon	33 years	-	-	-	-	B.3.2.2
Total number of cycles	394	-	-	-	-	B.3.2.2
Age	67.20 years	11.65	46.34	91.88	Gamma	B.3.3.1
Percentage male	48.10%	0.10	29.55%	66.93%	Beta	B.3.3.1
Discount rate costs	3.5%	-	-	-	-	B.3.2.2
Discount rate outcomes	3.5%	-	-	-	-	B.3.2.2
Drug acquisition costs						
Netarsudil-latanoprost acquisition cost per cycle	£17.05	-	-	-	-	B.3.5.1
Brinzolamide-timolol acquisition cost per cycle	£8.01	-	-	-	-	
Dorzolamide-timolol acquisition cost per cycle	£9.94	-	-	-	-	
Latanoprost-timolol acquisition cost per cycle	£11.37	-	-	-	-	
Bimatoprost-timolol acquisition cost per cycle	£15.03	-	-	-	-	
Brimonidine-timolol acquisition cost per cycle	£13.74	-	-	-	-	
Travoprost-timolol acquisition cost per cycle	£12.79	-	-	-	-	
Tafluprost-timolol acquisition cost per cycle	£14.71	-	-	-	-	
Brinzolamide-brimonidine acquisition cost per cycle	£11.24	-	-	-	-	
Drug administration costs						
Netarsudil-latanoprost administration cost per cycle	£0.00	0.00	0.00	0.00	Gamma	B.3.5.1
Brinzolamide-timolol administration cost per cycle	£0.00	0.00	0.00	0.00	Gamma	
Dorzolamide-timolol administration cost per cycle	£0.00	0.00	0.00	0.00	Gamma	
Latanoprost-timolol administration cost per cycle	£0.00	0.00	0.00	0.00	Gamma	
Bimatoprost-timolol administration cost per cycle	£0.00	0.00	0.00	0.00	Gamma	

Variable	Value	OWSA			Within PSA varied by	Reference to section in submission
		SE	Lower bound	Upper bound		
Brimonidine-timolol administration cost per cycle	£0.00	0.00	0.00	0.00	Gamma	
Travoprost-timolol administration cost per cycle	£0.00	0.00	0.00	0.00	Gamma	
Tafluprost-timolol administration cost per cycle	£0.00	0.00	0.00	0.00	Gamma	
Brinzolamide-brimonidine administration cost per cycle	£0.00	0.00	0.00	0.00	Gamma	
Concomitant therapies						
SLT unit cost	£167.10	33.42	108.14	238.68	Gamma	B.3.5.4
Trabeculectomy unit cost	£2,609.96	521.99	1,689.03	3,728.07	Gamma	
Proportion of patients with add-on SLT: <20% reduction in IOP	0.40%	0.00%	0.00%	1.00%	Beta	
Proportion of patients with add-on SLT: 20% - 30% reduction in IOP	0.36%	0.00%	0.00%	1.00%	Beta	
Proportion of patients with add-on SLT: >30% reduction in IOP	0.33%	0.00%	0.00%	0.00%	Beta	
Proportion of patients with add-on trabeculectomy: <20% reduction in IOP	1.61%	0.00%	1.00%	2.00%	Beta	
Proportion of patients with add-on trabeculectomy: 20% - 30% reduction in IOP	1.46%	0.00%	1.00%	2.00%	Beta	
Proportion of patients with add-on trabeculectomy: >30% reduction in IOP	1.34%	0.00%	1.00%	2.00%	Beta	
<20% reduction in IOP total cost	49.13	9.83	31.79	70.18	Gamma	B.3.4.6
20% - 30% reduction in IOP total cost	47.96	9.59	31.04	68.51	Gamma	
>30% reduction in IOP total cost	46.79	9.36	30.28	66.84	Gamma	
Netarsudil-latanoprost adverse event total cost (cycle 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Netarsudil-latanoprost adverse event total cost (cycle 2)						
Netarsudil-latanoprost adverse event total cost (cycle 3)						
Netarsudil-latanoprost adverse event total cost (cycle 4+)						
Brinzolamide-timolol adverse event total cost (cycle 1)	33.40	6.68	21.62	47.71	Gamma	
Brinzolamide-timolol adverse event total cost (cycle 2)	30.44	6.09	19.70	43.49	Gamma	
Brinzolamide-timolol adverse event total cost (cycle 3)	21.50	4.30	13.91	30.71	Gamma	
Brinzolamide-timolol adverse event total cost (cycle 4+)	0.00	0.00	0.00	0.00	Gamma	
Dorzolamide-timolol adverse event total cost (cycle 1)	42.93	8.59	27.78	61.33	Gamma	
Dorzolamide-timolol adverse event total cost (cycle 2)	39.97	7.99	25.87	57.10	Gamma	
Dorzolamide-timolol adverse event total cost (cycle 3)	29.88	5.98	19.33	42.67	Gamma	

Variable	Value	OWSA			Within PSA varied by	Reference to section in submission
		SE	Lower bound	Upper bound		
Dorzolamide-timolol adverse event total cost (cycle 4+)	0.01	0.00	0.00	0.01	Gamma	
Latanoprost-timolol adverse event total cost (cycle 1)	32.04	6.41	20.74	45.77	Gamma	
Latanoprost-timolol adverse event total cost (cycle 2)	31.92	6.38	20.66	45.60	Gamma	
Latanoprost-timolol adverse event total cost (cycle 3)	23.81	4.76	15.41	34.01	Gamma	
Latanoprost-timolol adverse event total cost (cycle 4+)	5.42	1.08	3.51	7.74	Gamma	
Tafluprost-timolol adverse event total cost (cycle 1)	38.43	7.69	24.87	54.90	Gamma	
Tafluprost-timolol adverse event total cost (cycle 2)	37.67	7.53	24.38	53.81	Gamma	
Tafluprost-timolol adverse event total cost (cycle 3)	24.10	4.82	15.60	34.42	Gamma	
Tafluprost-timolol adverse event total cost (cycle 4+)	5.41	1.08	3.50	7.73	Gamma	
Bimatoprost-timolol adverse event total cost (cycle 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Bimatoprost-timolol adverse event total cost (cycle 2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Bimatoprost-timolol adverse event total cost (cycle 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Bimatoprost-timolol adverse event total cost (cycle 4+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Brimonidine-timolol adverse event total cost (cycle 1)	56.62	11.32	36.64	80.88	Gamma	
Brimonidine-timolol adverse event total cost (cycle 2)	48.36	9.67	31.29	69.07	Gamma	
Brimonidine-timolol adverse event total cost (cycle 3)	26.45	5.29	17.12	37.79	Gamma	
Brimonidine-timolol adverse event total cost (cycle 4+)	0.01	0.00	0.00	0.01	Gamma	
Travoprost-timolol adverse event total cost (cycle 1)	36.26	7.25	23.47	51.80	Gamma	
Travoprost-timolol adverse event total cost (cycle 2)	35.50	7.10	22.97	50.71	Gamma	
Travoprost-timolol adverse event total cost (cycle 3)	19.21	3.84	12.43	27.44	Gamma	
Travoprost-timolol adverse event total cost (cycle 4+)	5.42	1.08	3.51	7.74	Gamma	
Brinzolamide-brimonidine adverse event total cost (cycle 1)	43.93	8.79	28.43	62.74	Gamma	
Brinzolamide-brimonidine adverse event total cost (cycle 2)	35.66	7.13	23.08	50.94	Gamma	
Brinzolamide-brimonidine adverse event total cost (cycle 3)	15.53	3.11	10.05	22.19	Gamma	
Brinzolamide-brimonidine adverse event total cost (cycle 4+)	0.00	0.00	0.00	0.00	Gamma	
Utility inputs						
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	B.3.4.6
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Netarsudil-latanoprost adverse event total disutility (cycle 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Netarsudil-latanoprost adverse event total disutility (cycle 2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Netarsudil-latanoprost adverse event total disutility (cycle 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Netarsudil-latanoprost adverse event total disutility (cycle 4+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Variable	Value	OWSA			Within PSA varied by	Reference to section in submission
		SE	Lower bound	Upper bound		
Brinzolamide-timolol adverse event total disutility (cycle 1)	0.01	0.00	0.00	0.01	Beta	
Brinzolamide-timolol adverse event total disutility (cycle 2)	0.00	0.00	0.00	0.00	Beta	
Brinzolamide-timolol adverse event total disutility (cycle 3)	0.00	0.00	0.00	0.00	Beta	
Brinzolamide-timolol adverse event total disutility (cycle 4+)	0.00	0.00	0.00	0.00	Beta	
Dorzolamide-timolol adverse event total disutility (cycle 1)	0.01	0.00	0.01	0.01	Beta	
Dorzolamide-timolol adverse event total disutility (cycle 2)	0.01	0.00	0.00	0.01	Beta	
Dorzolamide-timolol adverse event total disutility (cycle 3)	0.00	0.00	0.00	0.01	Beta	
Dorzolamide-timolol adverse event total disutility (cycle 4+)	0.00	0.00	0.00	0.00	Beta	
Latanoprost-timolol adverse event total disutility (cycle 1)	0.01	0.00	0.00	0.01	Beta	
Latanoprost-timolol adverse event total disutility (cycle 2)	0.01	0.00	0.00	0.01	Beta	
Latanoprost-timolol adverse event total disutility (cycle 3)	0.00	0.00	0.00	0.00	Beta	
Latanoprost-timolol adverse event total disutility (cycle 4+)	0.00	0.00	0.00	0.00	Beta	
Tafluprost-timolol adverse event total disutility (cycle 1)	0.01	0.00	0.00	0.01	Beta	
Tafluprost-timolol adverse event total disutility (cycle 2)	0.00	0.00	0.00	0.01	Beta	
Tafluprost-timolol adverse event total disutility (cycle 3)	0.00	0.00	0.00	0.00	Beta	
Tafluprost-timolol adverse event total disutility (cycle 4+)	0.00	0.00	0.00	0.00	Beta	
Bimatoprost-timolol adverse event total disutility (cycle 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Bimatoprost-timolol adverse event total disutility (cycle 2)						
Bimatoprost-timolol adverse event total disutility (cycle 3)						
Bimatoprost-timolol adverse event total disutility (cycle 4+)						
Brimonidine-timolol adverse event total disutility (cycle 1)	0.01	0.00	0.01	0.02	Beta	
Brimonidine-timolol adverse event total disutility (cycle 2)	0.01	0.00	0.00	0.01	Beta	
Brimonidine-timolol adverse event total disutility (cycle 3)	0.00	0.00	0.00	0.01	Beta	
Brimonidine-timolol adverse event total disutility (cycle 4+)	0.00	0.00	0.00	0.00	Beta	
Travoprost-timolol adverse event total disutility (cycle 1)	0.01	0.00	0.01	0.02	Beta	
Travoprost-timolol adverse event total disutility (cycle 2)	0.01	0.00	0.00	0.01	Beta	
Travoprost-timolol adverse event total disutility (cycle 3)	0.00	0.00	0.00	0.01	Beta	
Travoprost-timolol adverse event total disutility (cycle 4+)	0.00	0.00	0.00	0.00	Beta	
Brinzolamide-brimonidine adverse event total disutility (cycle 1)	0.01	0.00	0.00	0.01	Beta	
Brinzolamide-brimonidine adverse event total disutility (cycle 2)	0.00	0.00	0.00	0.00	Beta	

Variable	Value	OWSA			Within PSA varied by	Reference to section in submission
		SE	Lower bound	Upper bound		
Brinzolamide-brimonidine adverse event total disutility (cycle 3)	0.00	0.00	0.00	0.00	Beta	
Brinzolamide-brimonidine adverse event total disutility (cycle 4+)	0.00	0.00	0.00	0.00	Beta	

Abbreviations: IOP – Intraocular pressure; OWSA – One-way sensitivity analysis; PSA – Probability sensitivity analysis; SE – Standard error; SLT – Selective laser trabeculoplasty

B.3.8.2 Assumptions

Table 62 details the assumptions that underpin the cost-effectiveness model.

Table 62: Assumptions underpinning cost-effectiveness model

Factor	Assumed values	Justification
Time horizon	Lifetime (33 years)	NICE guidelines state that a time horizon must be long enough to capture differences in costs and health outcomes.[95] The mean age of patients in the MERCURY 3 trial is 67.2 years. Therefore a lifetime time horizon of 33 years is suitable to capture outcomes, as it is assumed that all patients will be dead by the age of 100 in accordance with standard modelling practice.[53] A lifetime time horizon was also used in existing models in the published literature (NICE guidelines 2017[96], Gazzard 2019[75]).
Cycle length	1-month (30.44 days)	This aligns with the MERCURY 3 trial, in which IOP was generally measured at monthly intervals. Using a 1-month cycle length allows for optimal granularity in model inputs and enables reflection of rapid reductions in IOP from baseline, as observed in the MERCURY 3 trial.
Half-cycle correction applied	Included in base case	A half-cycle correction was applied to costs and health outcomes in the Markov model to align with conventional modelling standards.
Health states	• <20% reduction in IOP from baseline • 20-30% reduction in IOP from baseline • >30% reduction in IOP from baseline • Death	IOP was deemed the most suitable outcome from which to define health states reflective of the long-term goals of POAG and OHT treatment. Clinically applicable target IOP ranges vary from patient to patient, dependent on the severity of their glaucoma. As such, defining health states based on absolute IOP thresholds was deemed unsuitable for this analysis. The structure of the economic model was designed to capture benefits in reductions in disease progression, and therefore higher QoL and lower costs associated, using health states defined by percentage change from baseline in IOP. The IOP reduction thresholds of <20%, 20-30%, and >30% were applied in the model based on published sources which applied 20% and 30% IOP reduction thresholds as indicators of treatment success, preventing progression, and a typical treatment target.[75,91–93] The thresholds further align with the suggested upper limit of initial target IOP for each eye, as per the Canadian Ophthalmological Society evidence-

Factor	Assumed values	Justification
		based clinical practice guidelines for glaucoma management.[94] Prior to model development, the proposed health states were validated with a UK clinical expert who confirmed the health state approach (IOP reduction from baseline) and thresholds were appropriate for patients with POAG and OHT.[90]
Model approach	Markov state transition cohort model	Treatment effectiveness is captured by distinct IOP reduction categories (<20%, 20-30%, >30%), which map to resource use, costs, and patient quality-of-life. Therefore, a Markov state transition cohort structure is appropriate to capture sustained response to treatment.
Background mortality	Background mortality data based on national life tables was applied in the model, with POAG and OHT considered to have no impact on mortality risk	In the economic model, only general background population mortality is applied; it is assumed that mortality is unaffected by POAG or OHT diagnosis and IOP percentage reduction. This methodology is in line with the NG81 cost-effectiveness model where throughout the model, individuals had a probability of dying which was age-dependent and independent from the stage of OHT or POAG.[39] This approach was also validated by a UK clinical expert.[102]
Baseline age	67.2 years	The mean age at which patients enter the model is informed by the ITT population in MERCURY 3.[53]
Proportion of males	48.1%	The proportion of males in the model is informed by the ITT population in MERCURY 3.[53]
Resource use per cycle	Values were sourced for one period only	Resource use per cycle was assumed to be constant for all cycles. This assumption was validated by a UK clinical expert.[102]
Market share	Within class and across class market shares are based on a UK sales data trend of December 2015 – December 2022. This analysis was conducted by Santen	It is assumed that sales data from December 2015 – December 2022 is reflective of the current market (in 2023). This selection of data was considered broad enough to reflect longer term trends, whilst still providing an up-to-date reflection of the current market.
Comparator unit dosing and treatment costs	It is assumed that a unit dose applies for one infected eye	When sourcing pack information from the BNF, it is assumed that a unit dose applies for one infected eye. When converting ml doses to drops, a 0.05 ml per drop conversion factor is applied. This value is based on commonly used values in the published literature.[131] Accordingly, it is assumed that for all ml dosed (non-unit dosed) comparators, treatment will be applied by ml with no wastage. This assumption and method was validated by a UK clinical expert.[102] It is important to note that the company has data on file supporting the use of a lower drop size for netarsudil-latanoprost which would reduce the overall cost of treatment. Hence, the assumption used here is conservative.

Factor	Assumed values	Justification
Administration costs	Administration costs are assumed to be negligible for all the FDC therapies	The assumption that administration costs are negligible for all the FDC therapies considered in the model is based on the fact that they are all self-administered eye drops.
Transition matrices and source of efficacy data	For the netarsudil-latanoprost and bimatoprost-timolol matrices, transition probabilities are informed by MERCURY 3 IPD.[53] An ITC was conducted to produce estimated transition counts for dorzolamide-timolol, brimonidine-timolol, and brinzolamide-brimonidine.[61,62] Efficacy data were unavailable for other FDCs, therefore efficacy was assumed equal to comparators of the same drug class. Therefore for the following PGA+BB comparators, efficacy was assumed equal to bimatoprost-timolol: • Latanoprost-timolol • Tafluprost-timolol • Travoprost-timolol For the following CAI + BB comparator, efficacy was assumed equal to dorzolamide-timolol: • Brinzolamide-timolol	MERCURY 3 is the most appropriate source for netarsudil-latanoprost and bimatoprost-timolol efficacy data as this reflects the population of interest for this appraisal. The ITC attempts to reduce bias caused by the lack of a head-to-head trial comparing netarsudil-latanoprost to comparators of interest. Comparators in the same drug classes have an equivalent mechanism of action and are therefore expected to be of similar efficacy.
Transition matrix extrapolation: Average method applied in the base case	The Average method, employed in the base case, applies an average of the baseline-cycle 3 transition probability values to all remaining cycles. This assumes that patient improvement/worsening in IOP post-cycle 3 follows the same trend observed in cycles 1 to 3.	The 'Average' method is considered reflective of clinical expectations, as confirmed by a UK clinical expert.
Concomitant treatments	The uptake of SLT and/or trabeculectomy was assumed to be consistent across the intervention and all comparators. No other concomitant treatments were included in the model.	In the absence of treatment-specific data, it was assumed that the uptake of SLT and/or trabeculectomy was consistent across the intervention and all comparators. Uptake for SLT and/or trabeculectomy was based on NHS secondary care data, applying the 2022 rates to all years of the model for the '<20% reduction in IOP' health state. A 10% multiplier

Factor	Assumed values	Justification
		decrement was applied for the other health states to reflect reduced uptake from a decreasing IOP. It was also assumed, in line with MERCURY 3, that no other concomitant treatments would be taken by patients and impact costs, efficacy, or safety outcomes.
Patient utility	HSUVs were estimated using MERCURY 3 trial data, by mapping SF-36 observations to EQ-5D utility indices, using a mapping algorithm published in Ara *et al.* (2008). Mean utilities were then estimated for each health state and applied directly in the model. Utilities for each AE were applied in the model for their average duration observed in the MERCURY 3 trial. If AEs did not occur in the trial (abnormal vision, conjunctival bleeding, eyelash discolouration) it was assumed conservatively, that the AEs were one cycle long. If an AE end date was not reported, a value of 120 days was applied, translating to application in all cycles (cycle 4+/treatment duration). AE durations were rounded to the nearest cycle length (i.e., nearest 30 days).	Ara and Brazier (2008)[97] was considered appropriate for mapping SF-36 data, as the algorithms were developed using a dataset collected in the UK and included patient observations with various indications. The Ara and Brazier (2008)[97] method was selected for the base case, due to its alignment with existing utility values in the literature. An equivalent regression method (Brazier and Roberts 2004) as Ara and Brazier (2008) had previously been utilised for mapping SF-36 data to EQ-5D as published in NICE HST5.[116,117] In the absence of data, the assumption that an AE will last one cycle is conservative. If an AE end date was not supplied, it is expected that the AE was ongoing at the end of the study period and therefore application in all cycles is reasonable.
Caregiver costs and quality-of-life	Not included in the economic analysis.	As confirmed by a UK clinical expert.

Abbreviations: AE– Adverse event; BB – Beta blocker; BNF– British National Formulary; CEM – Cost-effectiveness model; COAG – Chronic open-angle glaucoma; EQ-5D – EuroQol 5 Dimensions; IOP – Intraocular pressure; ITT– Intention-to-treat; NICE, National Institute for Health and Care Excellence; OAG– open-angle glaucoma; OHT– Ocular hypertension; PGA – Prostaglandin analogue; POAG – Primary open-angle glaucoma; SF-36 – Short Form 36; UK, United Kingdom

B.3.9 Base-case results

B.3.9.1 Base-case incremental CEA results

This section presents the base-case results of the CEA comparing netarsudil-latanoprost to FDC comparators in a population of patients with POAG or OHT. Base-case results are presented using the list price for netarsudil-latanoprost, as described in section B.3.5.1.

Deterministic results showing incremental costs, life years gained (LYG) and QALYs for each FDC comparator versus netarsudil-latanoprost is presented in Table 63. An incremental analysis showing the total costs, LYG, QALYs, ICER versus baseline and ICER versus previously shown comparator for each FDC therapy is presented in Table 64.

In the deterministic base-case analysis, netarsudil-latanoprost was associated with lower average costs ([redacted]) when compared to all FDC comparators (except for brinzolamide-timolol), indicating that netarsudil-latanoprost is cost-saving versus the FDC comparators over a lifetime time horizon.

Compared to netarsudil-latanoprost, brinzolamide-brimonidine was associated with incremental costs of [redacted] and incremental QALYs of [redacted], resulting in an ICER of £4,079. Clinical experts have indicated that brinzolamide-brimonidine is not commonly used in UK clinical practice in this population; it is typically used as a third- or fourth-line treatment for patients who have tolerability issues. This is discussed further in section B.3.12.

For the comparisons of netarsudil-latanoprost to travoprost-timolol, latanoprost-timolol and brimonidine-timolol, the large ICERs for these comparators versus netarsudil-latanoprost are a result of very small incremental QALYs between the interventions. Compared to netarsudil-latanoprost:

- Travoprost-timolol was associated with incremental costs of [redacted] and incremental QALYs of [redacted], resulting in an ICER of £1,778,704.
- Latanoprost-timolol was associated with incremental costs of [redacted] and incremental QALYs of [redacted], resulting in an ICER of £578,782.
- Brimonidine-timolol was associated with incremental costs of [redacted] and incremental QALYs of [redacted], resulting in an ICER of £172,645.

Notably, the greatest difference in incremental QALYs between an FDC comparator versus netarsudil-latanoprost was [redacted] (versus brinzolamide-brimonidine and brinzolamide-timolol).

The extremely small differences in incremental QALYs indicate negligible differences in treatment efficacy between all therapies over a 33-year time horizon, supporting the consideration of a cost-comparison approach rather than a full incremental CEA.

Disaggregated base-case results are presented in Appendix J.

Table 63: Deterministic base-case incremental analysis (incremental results of each comparator vs. netarsudil-latanoprost)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs. incremental QALYs
Netarsudil-latanoprost	[redacted]	13.036	[redacted]	-	-	-	-
Brinzolamide-timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominating
Travoprost-timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	1,778,704
Dorzolamide-timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	688
Latanoprost-timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	578,782
Tafluprost-timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	66,858
Bimatoprost-timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	60,284
Brimonidine-timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	172,645
Brinzolamide-brimonidine	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	4,079

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Table 64: Deterministic base-case results (incremental results vs. treatment with lowest total costs)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs. incremental QALYs
Brinzolamide-timolol	[redacted]	13.036	[redacted]	-	-	-	-
Netarsudil-latanoprost	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominated
Dorzolamide-timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominated
Brinzolamide-brimonidine	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	342,699
Brimonidine-timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominated
Bimatoprost-timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominated
Latanoprost-timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominated
Travoprost-timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominated
Tafluprost-timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominated

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

B.3.10 Sensitivity analysis

Probabilistic sensitivity analyses (PSA) and one-way sensitivity analysis (OWSA) have been performed and are presented in section B.3.10.1 and B.3.10.2, respectively. Key areas of uncertainty tested in sensitivity analyses included health state costs, adverse event costs and utility values. Scenario analyses conducted in section B.3.10.3 explore parameter and scenario uncertainty.

B.3.10.1 Probabilistic sensitivity analysis

A PSA was conducted to estimate the uncertainties in the key model parameters. The analysis involved varying the inputs by randomly assigning a parameter value from predefined uncertainty distributions.

This was performed for each parameter simultaneously over multiple iterations, and the resulting incremental cost and QALY predictions were recorded. To ensure stability in results, it was decided to run 10,000 iterations for the base-case analysis.

Where the standard errors for the parameters were unknown, they were assumed to be 20% of the parameter value for the purposes of defining the PSA distributions. For event rates and utilities, a beta distribution was used to restrict draws between 0 and 1. For costs and resource use estimates, a gamma distribution was fitted to prevent values less than zero.

Mean incremental results were recorded and illustrated through an incremental cost-effectiveness plane (ICEP). In addition, a cost-effectiveness acceptability curve (CEAC) was plotted.

Table 65 shows the mean results of the PSA comparing the FDC with the lowest treatment cost versus all other comparators. Probabilistic costs, LYs and QALYs are generally consistent with the deterministic results. Netarsudil-latanoprost was associated with a total cost of [redacted] and mean total QALYs of [redacted]. The mean probabilistic results are similar to the base case for all comparators.

The ICEP is presented in Figure 15, and shows that netarsudil-latanoprost is [redacted] than all FDC comparators, except for brinzolamide-timolol, in which case netarsudil-latanoprost is [redacted], with mean PSA points displayed in the [redacted].

Table 65: PSA incremental results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Brinzolamide-timolol	[redacted]	12.602	[redacted]	-	-	-	-
Dorzolamide-timolol	[redacted]	12.602	[redacted]	[redacted]	0.000	[redacted]	Dominated
Netarsudil-latanoprost	[redacted]	12.602	[redacted]	[redacted]	0.000	[redacted]	Dominated
Brinzolamide-brimonidine	[redacted]	12.602	[redacted]	[redacted]	0.000	[redacted]	346,853
Brimonidine-timolol	[redacted]	12.602	[redacted]	[redacted]	0.000	[redacted]	Dominated
Bimatoprost-timolol	[redacted]	12.602	[redacted]	[redacted]	0.000	[redacted]	Dominated
Latanoprost-timolol	[redacted]	12.602	[redacted]	[redacted]	0.000	[redacted]	Dominated
Travoprost-timolol	[redacted]	12.602	[redacted]	[redacted]	0.000	[redacted]	Dominated
Tafluprost-timolol	[redacted]	12.602	[redacted]	[redacted]	0.000	[redacted]	Dominated

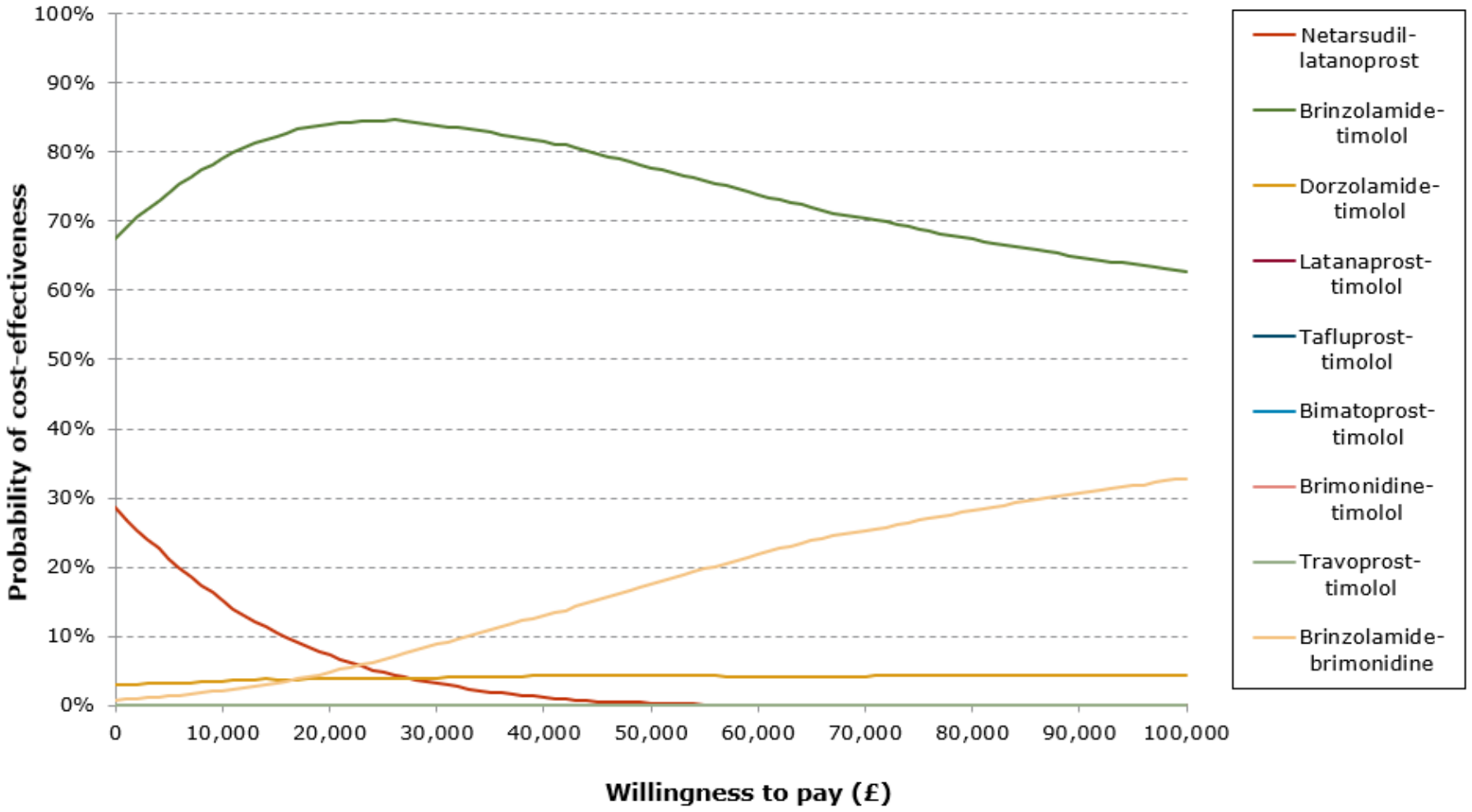
Abbreviations: ICER – Incremental cost-effectiveness ratio; QALYs – Quality-adjusted life years

Figure 15: ICEP for netarsudil-latanoprost versus FDC comparators

Abbreviations: FDC – Fixed-dose combination; ICEP – Incremental cost-effectiveness plane; PSA – Probabilistic sensitivity analysis; QALYs – Quality-adjusted life years

The CEAC is displayed in Figure 16 to illustrate the probability of netarsudil-latanoprost being cost-effective compared to comparators at various willingness-to-pay thresholds.

Figure 16: CEAC for netarsudil-latanoprost versus FDC comparators



Abbreviations: CEAC – Cost-effectiveness acceptability curve; FDC – Fixed-dose combination

B.3.10.2 Deterministic sensitivity analysis

A OWSA was used to assess the effect of parameter variation on net monetary benefit (NMB). The OWSA was performed using a SE approach. Where the SE was not available for a parameter, the SE was assumed to be 20% of the mean value. Based on its mean and the SE, the parameter was then varied using a 95% confidence interval based on the distribution of the parameter.

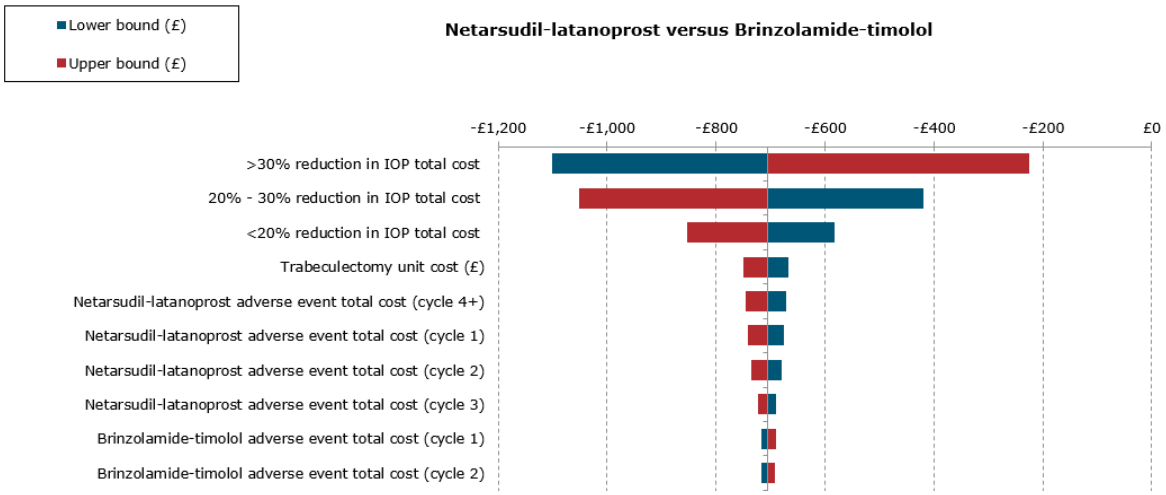
A tornado diagram was developed to graphically present the parameters for all variables which have the greatest effect on the NMB, at a willingness-to-pay (WTP) threshold of £30,000 per QALY.

The OWSA was performed for netarsudil-latanoprost compared to each FDC comparator in the model. The results are presented in the subsections below.

B.3.10.2.1 Netarsudil-latanoprost versus brinzolamide-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB, for the comparison of netarsudil-latanoprost with brinzolamide-timolol is presented in Figure 17, with tabulated results presented in Table 66. The model was most sensitive to the health state costs.

Figure 17: OWSA tornado diagram for netarsudil-latanoprost versus brinzolamide-timolol: NMB



Abbreviations: IOP – Intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Table 66. Tabulated OWSA results for netarsudil-latanoprost versus brinzolamide-timolol: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
>30% reduction in IOP total cost	-£1,099	-£226	£874
20% - 30% reduction in IOP total cost	-£419	-£1,051	£632
<20% reduction in IOP total cost	-£583	-£853	£270
Trabeculectomy unit cost (£)	-£668	-£749	£80
Netarsudil-latanoprost adverse event total cost (cycle 4+)	-£672	-£745	£73

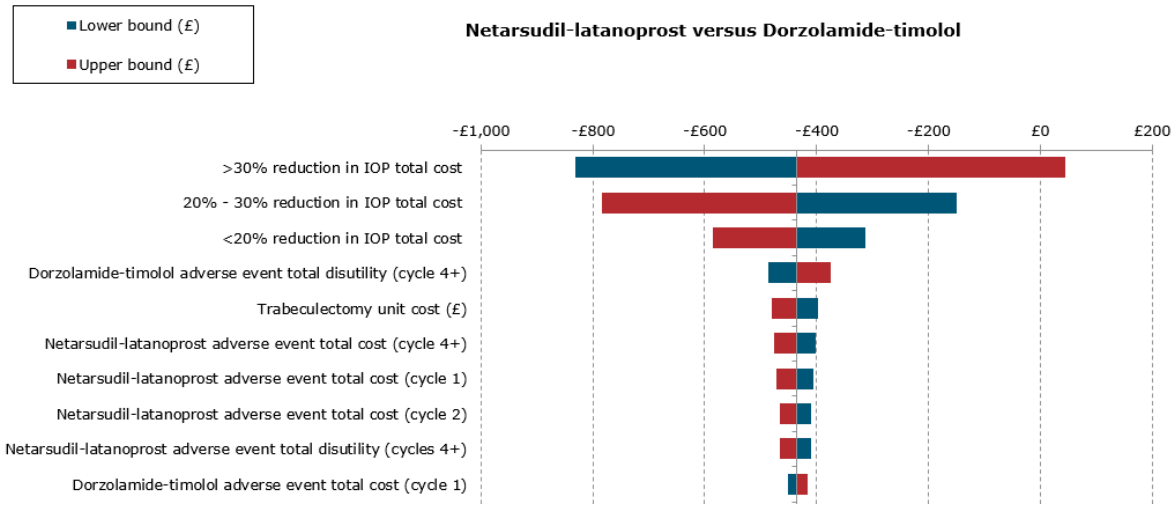
Netarsudil-latanoprost adverse event total cost (cycle 1)	-£676	-£740	£64
Netarsudil-latanoprost adverse event total cost (cycle 2)	-£680	-£735	£54
Netarsudil-latanoprost adverse event total cost (cycle 3)	-£690	-£722	£32
Brinzolamide-timolol adverse event total cost (cycle 1)	-£716	-£691	£26
Brinzolamide-timolol adverse event total cost (cycle 2)	-£715	-£692	£23

Abbreviations: IOP – Intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

B.3.10.2.2 Netarsudil-latanoprost versus dorzolamide-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB for the comparison of netarsudil-latanoprost with dorzolamide-timolol is presented in Figure 18, with tabulated results presented in Table 67. The model was most sensitive to the health state costs.

Figure 18: OWSA tornado diagram for netarsudil-latanoprost versus dorzolamide-timolol: NMB



Abbreviations: IOP – Intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Table 67. Tabulated OWSA results for netarsudil-latanoprost versus dorzolamide-timolol: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
>30% reduction in IOP total cost	-£830	£44	£874
20% - 30% reduction in IOP total cost	-£150	-£782	£632
<20% reduction in IOP total cost	-£313	-£584	£270
Dorzolamide-timolol adverse event total disutility (cycle 4+)	-£485	-£375	£110
Trabeculectomy unit cost (£)	-£399	-£479	£80
Netarsudil-latanoprost adverse event total cost (cycle 4+)	-£402	-£475	£73
Netarsudil-latanoprost adverse event total cost (cycle 1)	-£407	-£470	£64
Netarsudil-latanoprost adverse event total cost (cycle 2)	-£411	-£465	£54

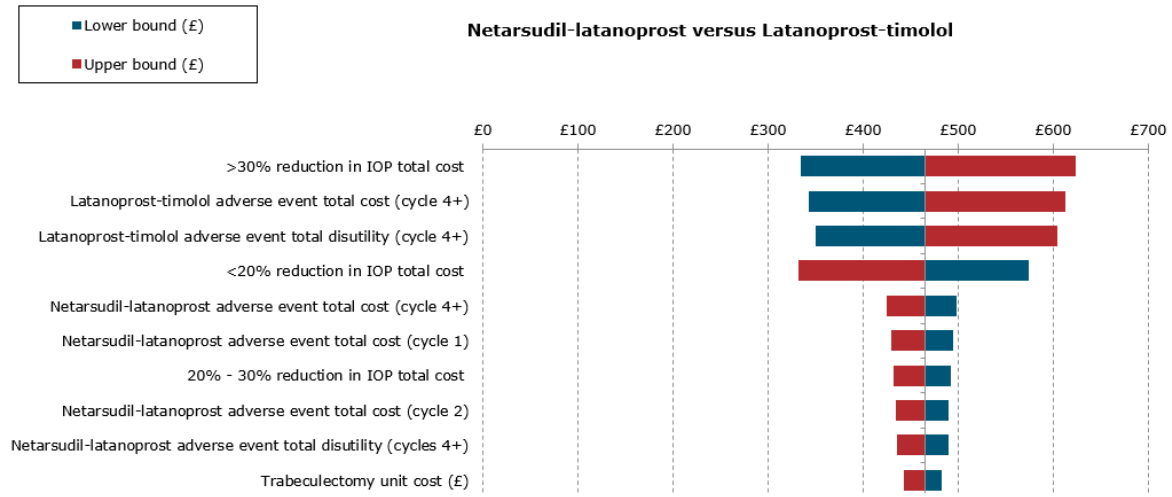
Netarsudil-latanoprost adverse event total disutility (cycles 4+)	-£412	-£464	£52
Dorzolamide-timolol adverse event total cost (cycle 1)	-£450	-£417	£33

Abbreviations: NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

B.3.10.2.3 Netarsudil-latanoprost versus latanoprost-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB for the comparison of netarsudil-latanoprost with latanoprost-timolol is presented in Figure 19, with tabulated results presented in Table 68. The model was most sensitive to the health state cost for the >30% reduction in IOP health state and the total adverse event cost and disutility for latanoprost-timolol for cycle 4+.

Figure 19: OWSA tornado diagram for netarsudil-latanoprost versus latanoprost-timolol: NMB



Abbreviations: IOP – Intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Table 68. Tabulated OWSA results for netarsudil-latanoprost versus latanoprost-timolol: NMB

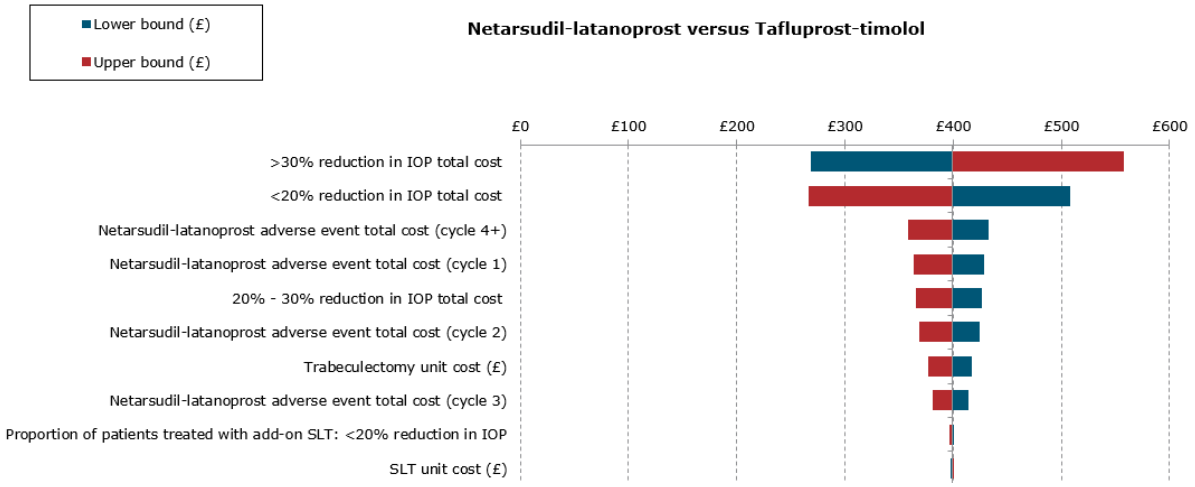
Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
>30% reduction in IOP total cost	£335	£623	£288
Latanoprost-timolol adverse event total cost (cycle 4+)	£344	£612	£268
Latanoprost-timolol adverse event total disutility (cycle 4+)	£351	£605	£254
<20% reduction in IOP total cost	£574	£333	£241
Netarsudil-latanoprost adverse event total cost (cycle 4+)	£498	£425	£73
Netarsudil-latanoprost adverse event total cost (cycle 1)	£494	£430	£64
20% - 30% reduction in IOP total cost	£492	£433	£60
Netarsudil-latanoprost adverse event total cost (cycle 2)	£490	£435	£54
Netarsudil-latanoprost adverse event total disutility (cycles 4+)	£489	£437	£52
Trabeculectomy unit cost (£)	£483	£444	£38

Abbreviations: IOP – Intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

B.3.10.2.4 Netarsudil-latanoprost versus tafluprost-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB for the comparison of netarsudil-latanoprost with tafluprost-timolol is presented in Figure 20, with tabulated results presented in Table 69. The model was most sensitive to the health state costs for the >30% and <20% reduction in IOP health states and the netarsudil-latanoprost adverse event total cost for cycle 4+.

Figure 20: OWSA tornado diagram for netarsudil-latanoprost versus tafluprost-timolol: NMB



Abbreviations: IOP – Intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Table 69. Tabulated OWSA results for netarsudil-latanoprost versus tafluprost-timolol: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
>30% reduction in IOP total cost	£269	£557	£288
<20% reduction in IOP total cost	£508	£267	£241
Netarsudil-latanoprost adverse event total cost (cycle 4+)	£432	£359	£73
Netarsudil-latanoprost adverse event total cost (cycle 1)	£428	£364	£64
20% - 30% reduction in IOP total cost	£426	£366	£60
Netarsudil-latanoprost adverse event total cost (cycle 2)	£424	£369	£54
Trabeculectomy unit cost (£)	£416	£378	£38
Netarsudil-latanoprost adverse event total cost (cycle 3)	£413	£381	£32
Proportion of patients treated with add-on SLT: <20% reduction in IOP	£400	£397	£3
SLT unit cost (£)	£398	£400	£1

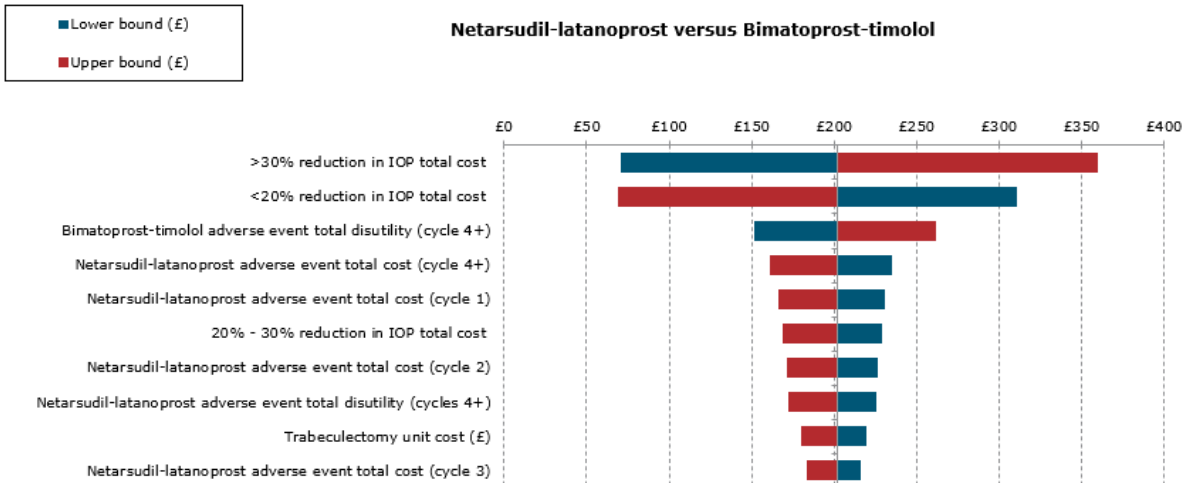
Abbreviations: IOP – Intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

B.3.10.2.5 Netarsudil-latanoprost versus bimatoprost-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB for the comparison of netarsudil-latanoprost with bimatoprost-timolol is presented in Figure 21, with tabulated results presented in Table 70. The model was most sensitive to the health state

costs for the >30% and <20% reduction in IOP health states and the bimatoprost-timolol adverse event total disutility for cycle 4+.

Figure 21: OWSA tornado diagram for netarsudil-latanoprost versus bimatoprost-timolol: NMB



Abbreviations: IOP – Intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Table 70: Tabulated OWSA results for netarsudil-latanoprost versus bimatoprost-timolol: NMB

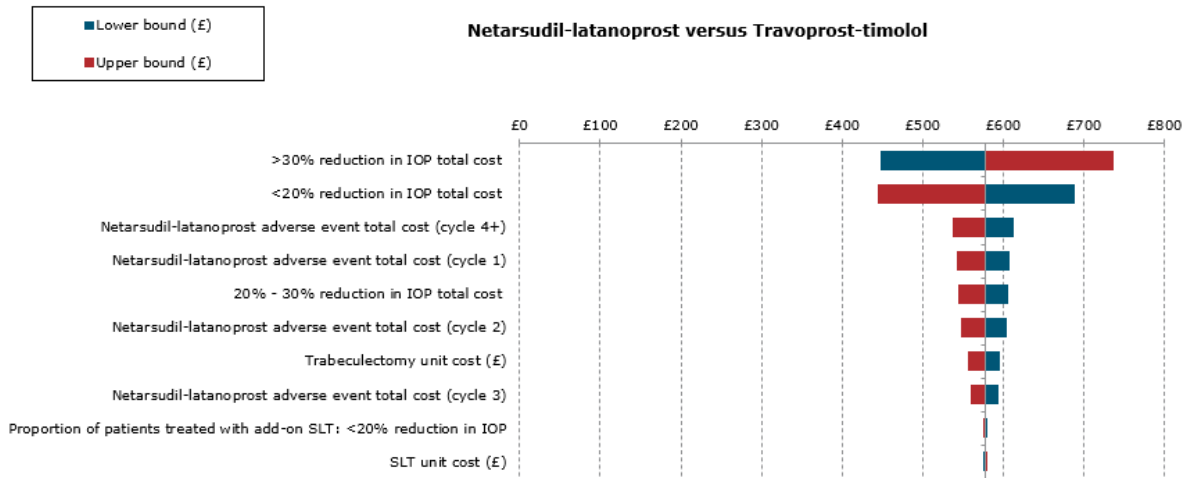
Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
>30% reduction in IOP total cost	£71	£360	£288
<20% reduction in IOP total cost	£311	£69	£241
Bimatoprost-timolol adverse event total disutility (cycle 4+)	£152	£262	£110
Netarsudil-latanoprost adverse event total cost (cycle 4+)	£235	£161	£73
Netarsudil-latanoprost adverse event total cost (cycle 1)	£230	£167	£64
20% - 30% reduction in IOP total cost	£228	£169	£60
Netarsudil-latanoprost adverse event total cost (cycle 2)	£226	£172	£54
Netarsudil-latanoprost adverse event total disutility (cycles 4+)	£225	£173	£52
Trabeculectomy unit cost (£)	£219	£181	£38
Netarsudil-latanoprost adverse event total cost (cycle 3)	£216	£184	£32

Abbreviations: IOP – Intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

B.3.10.2.6 Netarsudil-latanoprost versus travoprost-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB for the comparison of netarsudil-latanoprost with travoprost-timolol is presented in Figure 22, with tabulated results presented in Table 71. The model was most sensitive to the health state cost for the >30% reduction in IOP health state and the travoprost-timolol adverse event total cost and adverse event totally disutility for cycle 4+.

Figure 22: OWSA tornado diagram for netarsudil-latanoprost versus travoprost-timolol: NMB



Abbreviations: NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Table 71: Tabulated OWSA results for netarsudil-latanoprost versus travoprost-timolol: NMB

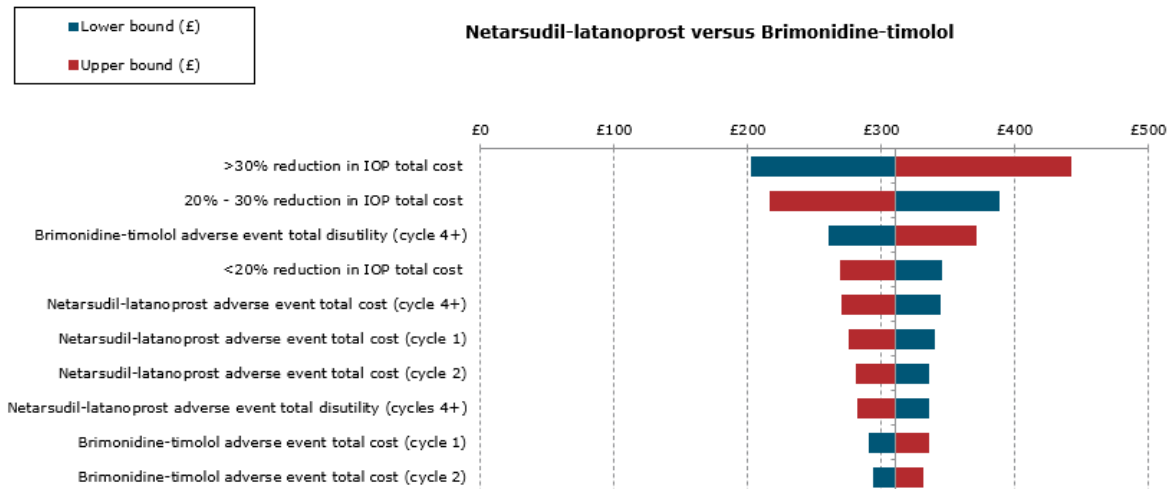
Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
>30% reduction in IOP total cost	£448	£736	£288
<20% reduction in IOP total cost	£687	£446	£241
Netarsudil-latanoprost adverse event total cost (cycle 4+)	£611	£538	£73
Netarsudil-latanoprost adverse event total cost (cycle 1)	£607	£543	£64
20% - 30% reduction in IOP total cost	£605	£546	£60
Netarsudil-latanoprost adverse event total cost (cycle 2)	£603	£548	£54
Trabeculectomy unit cost (£)	£596	£557	£38
Netarsudil-latanoprost adverse event total cost (cycle 3)	£593	£561	£32
Proportion of patients treated with add-on SLT: <20% reduction in IOP	£580	£577	£3
SLT unit cost (£)	£578	£579	£1

Abbreviations: NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

B.3.10.2.7 Netarsudil-latanoprost versus brimonidine-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB for the comparison of netarsudil-latanoprost with brimonidine-timolol is presented in Figure 23, with tabulated results presented in Table 72. The model was most sensitive to the health state costs for all health states and the brimonidine-timolol adverse event total disutility for cycle 4+.

Figure 23: OWSA tornado diagram for netarsudil-latanoprost versus brimonidine-timolol: NMB



Abbreviations: NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Table 72: Tabulated OWSA results for netarsudil-latanoprost versus brimonidine-timolol: NMB

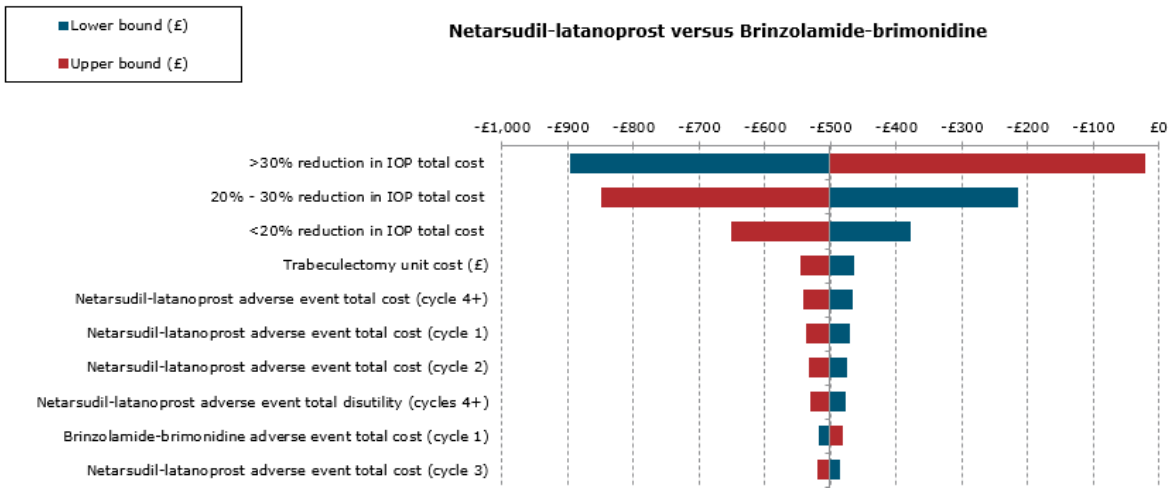
Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
>30% reduction in IOP total cost	£203	£442	£238
20% - 30% reduction in IOP total cost	£388	£217	£171
Brimonidine-timolol adverse event total disutility (cycle 4+)	£261	£371	£110
<20% reduction in IOP total cost	£345	£270	£75
Netarsudil-latanoprost adverse event total cost (cycle 4+)	£344	£271	£73
Netarsudil-latanoprost adverse event total cost (cycle 1)	£340	£276	£64
Netarsudil-latanoprost adverse event total cost (cycle 2)	£336	£281	£54
Netarsudil-latanoprost adverse event total disutility (cycles 4+)	£335	£282	£52
Brimonidine-timolol adverse event total cost (cycle 1)	£291	£335	£44
Brimonidine-timolol adverse event total cost (cycle 2)	£294	£331	£37

Abbreviations: NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

B.3.10.2.8 Netarsudil-latanoprost versus brinzolamide-brimonidine

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB for the comparison of netarsudil-latanoprost with brinzolamide-brimonidine is presented in Figure 24, with tabulated results presented in Table 73. The model was most sensitive to the health state costs.

Figure 24: OWSA tornado diagram for netarsudil-latanoprost versus brinzolamide-brimonidine: NMB



Abbreviations: NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Table 73: Tabulated OWSA results for netarsudil-latanoprost versus brinzolamide-brimonidine: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
>30% reduction in IOP total cost	-£896	-£22	£874
20% - 30% reduction in IOP total cost	-£216	-£848	£632
<20% reduction in IOP total cost	-£379	-£649	£270
Trabeculectomy unit cost (£)	-£465	-£545	£80
Netarsudil-latanoprost adverse event total cost (cycle 4+)	-£468	-£541	£73
Netarsudil-latanoprost adverse event total cost (cycle 1)	-£472	-£536	£64
Netarsudil-latanoprost adverse event total cost (cycle 2)	-£477	-£531	£54
Netarsudil-latanoprost adverse event total disutility (cycles 4+)	-£477	-£530	£52
Brinzolamide-brimonidine adverse event total cost (cycle 1)	-£516	-£483	£34
Netarsudil-latanoprost adverse event total cost (cycle 3)	-£487	-£519	£32

Abbreviations: NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

B.3.10.3 Scenario analysis

Various scenario analyses were conducted to investigate the impact of using alternative assumptions. These include:

- Varying the BNF costs considered (drug tariff price and NHS indicative price)
- Varying the compliance rate (90% and 80% for all comparators)
- Varying the long-term efficacy extrapolation method (LOCF and final)
- Varying the persistence rate (set equal to netarsudil-latanoprost for all comparators, except bimatoprost-timolol)
- Not applying age-adjusted utilities
- Varying the discount rate (1.5% costs and 3.5% outcomes, 3.5% costs and 1.5% outcomes, and 1.5% costs and 1.5% outcomes)
- Varying the time horizon (5 years and 15 years)
- Varying transition probabilities for brinzolamide-brimonidine (set equal to bimatoprost-timolol)
- Varying the transition probability method (MAIC output, STC excluding OHT patients, and STC excluding 08:00 IOP data)
- Varying the adverse event probabilities (base case rate doubled and tripled)
- Varying the QoL mapping method (Rowen *et al*. 2009)

B.3.10.3.1 Scenario analysis varying the BNF costs considered

A scenario analysis was conducted varying the BNF costs considered. The scenarios explored were drug tariff price and NHS indicative price (Table 74).

Table 74: Scenario analysis varying the BNF costs considered (incremental results vs. treatment with lowest total costs)

BNF costs considered	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
Drug tariff price	Brinzolamide-timolol	-	-	-	-	-
	Dorzolamide-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Netarsudil-latanoprost	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide-brimonidine	[redacted]	0.000	[redacted]	657,553	607,990
	Latanoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brimonidine-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
NHS indicative price	Brinzolamide-timolol	-	-	-	-	-
	Netarsudil-latanoprost	[redacted]	0.000	[redacted]	Dominated	Dominated
	Dorzolamide-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide-brimonidine	[redacted]	0.000	[redacted]	342,699	279,033
	Brimonidine-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Latanoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NHS – National Health Service; QALYs – Quality-adjusted life years

B.3.10.3.2 Scenario analysis varying the compliance rate

A scenario analysis was conducted varying the compliance rate of all comparators, to explore the impact of applying a reduced compliance rate. The compliance rates explored were 90% and 80%, relative to a 100% compliance rate at baseline (Table 75).

Table 75: Scenario analysis varying the compliance rate (incremental results vs. treatment with lowest total costs)

Compliance rate	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
90% for all comparators	Brinzolamide and timolol	-	-	-	-	-
	Dorzolamide and timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Roclanda	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide and brimonidine	[redacted]	0.000	[redacted]	309,896	262,801
	Brimonidine and timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost and timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Latanoprost and timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost and Timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost and timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
80% for all comparators	Brinzolamide and timolol	-	-	-	-	-
	Dorzolamide and timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide and brimonidine	[redacted]	0.000	[redacted]	277,093	307,177
	Roclanda	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brimonidine and timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost and timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Latanoprost and timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost and Timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost and timolol	[redacted]	0.000	[redacted]	Dominated	Dominated

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

B.3.10.3.3 Scenario analysis varying the extrapolation method for long-term efficacy estimates

A scenario analysis was conducted varying the extrapolation method used to generate long-term efficacy. The extrapolation methods explored were LOCF and assuming patients remain in their final health state (Table 76).

Table 76: Scenario analysis varying the extrapolation method for long-term efficacy estimates (incremental results vs. treatment with lowest total costs)

Extrapolation method	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
LOCF	Brinzolamide-timolol	-	-	-	-	-
	Netarsudil-latanoprost	[redacted]	0.000	[redacted]	Dominated	Dominated
	Dorzolamide-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide-brimonidine	[redacted]	0.000	[redacted]	342,699	452,347
	Brimonidine-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Latanoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
Final	Brinzolamide-timolol	-	-	-	-	-
	Netarsudil-latanoprost	[redacted]	0.000	[redacted]	Dominated	Dominated
	Dorzolamide-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide-brimonidine	[redacted]	0.000	[redacted]	342,699	327,927
	Brimonidine-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Latanoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated

Abbreviations: ICER – Incremental cost-effectiveness ratio; LOCF – Last observation carried forward; LYG – Life years gained; QALYs – Quality-adjusted life years

B.3.10.3.4 Scenario analysis varying the persistence rate

A scenario analysis was conducted varying the persistence rate of each comparator. In this scenario, the persistence rate for all comparators, except bimatoprost-timolol, was set equal to the persistence rate of netarsudil-latanoprost (Table 77).

Table 77: Scenario analysis varying the persistence rate (incremental results vs. treatment with lowest total costs)

Persistence rate	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
Persistence rate for all comparators (except bimatoprost-timolol) set equal to the persistence rate for netarsudil-latanoprost	Brinzolamide-timolol	-	-	-	-	-
	Dorzolamide-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide-brimonidine	[redacted]	0.000	[redacted]	122,245	130,006
	Latanoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brimonidine-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Netarsudil-latanoprost	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

B.3.10.3.5 Scenario analysis not applying age-adjusted utilities

A scenario analysis was conducted where age-adjusted utilities were not applied (Table 78).

Table 78: Scenario analysis not applying age-adjusted utilities (incremental results vs. treatment with lowest total costs)

Age-adjusted utilities applied?	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)

No	Brinzolamide-timolol	-	-	-	-	-
	Netarsudil-latanoprost	[redacted]	0.000	[redacted]	Dominated	Dominated
	Dorzolamide-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide-brimonidine	[redacted]	0.000	[redacted]	342,699	325,605
	Brimonidine-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Latanoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

B.3.10.3.6 Scenario analysis varying the discount rate

A scenario analysis was conducted varying the discount rate, to explore the impact of applying a reduced rate to future costs and outcomes. The discount rate combinations explored were: 1.5% costs and 3.5% outcomes, 3.5% costs and 1.5% outcomes and 1.5% costs and 1.5% outcomes, relative to a 3.5% discount rate at baseline for both costs and outcomes (Table 79).

Table 79: Scenario analysis varying the discount rate (incremental results vs. treatment with lowest total costs)

Discount rate	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)

1.5% costs and 3.5% outcomes	Brinzolamide-timolol	-	-	-	-	-
	Netarsudil-latanoprost	[redacted]	0.000	[redacted]	Dominated	Dominated
	Dorzolamide-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide-brimonidine	[redacted]	0.000	[redacted]	373,624	324,227
	Brimonidine-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Latanoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
3.5% costs and 1.5% outcomes	Brinzolamide-timolol	-	-	-	-	-
	Netarsudil-latanoprost	[redacted]	0.000	[redacted]	Dominated	Dominated
	Dorzolamide-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide-brimonidine	[redacted]	0.000	[redacted]	342,699	262,197
	Brimonidine-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Latanoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
1.5% costs and 1.5% outcomes	Brinzolamide-timolol	-	-	-	-	-
	Netarsudil-latanoprost	[redacted]	0.000	[redacted]	Dominated	Dominated
	Dorzolamide-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide-brimonidine	[redacted]	0.000	[redacted]	373,624	384,589
	Brimonidine-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Latanoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

B.3.10.3.7 Scenario analysis varying the time horizon

A scenario analysis was conducted changing the time horizon to 5 and 15 years (Table 80).

Table 80: Scenario analysis varying the time horizon (incremental results vs. treatment with lowest total costs)

Time horizon	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
5 years	Brinzolamide-timolol	-	-	-	-	-
	Dorzolamide-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide-brimonidine	[redacted]	0.000	[redacted]	215,386	212,716
	Roclanda	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brimonidine-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Latanoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
15 years	Brinzolamide-timolol	-	-	-	-	-
	Netarsudil-latanoprost	[redacted]	0.000	[redacted]	Dominated	Dominated
	Dorzolamide-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide-brimonidine	[redacted]	0.000	[redacted]	328,600	295,469
	Brimonidine-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Latanoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

B.3.10.3.8 Scenario analysis varying the transition probabilities for brinzolamide-brimonidine

A scenario analysis was conducted to change the transition probabilities for brinzolamide-brimonidine to be equal to bimatoprost-timolol (Table 81).

Table 81: Scenario analysis varying the brinzolamide-brimonidine transition probabilities (incremental results vs. treatment with lowest total costs)

Brinzolamide-brimonidine transition probabilities	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
Equal to bimatoprost-timolol	Brinzolamide-timolol	-	-	-	-	-
	Netarsudil-latanoprost	[redacted]	0.000	[redacted]	Dominated	Dominated
	Dorzolamide-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide-brimonidine	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brimonidine-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Latanoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

B.3.10.3.9 Scenario analysis varying the transition probability method

Scenario analyses were conducted to change the transition probabilities for all comparators. Three methods were applied; using the base-case MAIC results, using the STC results but excluding POAG patients, and using the STC results but excluding the 8am data (Table 82).

Table 82: Scenario analysis varying the transition probability method (incremental results vs. treatment with lowest total costs)

Transition probability method	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)

MAIC and base-case settings	Brimonidine-timolol	-	-	-	-	-
	Brinzolamide-timolol	[redacted]	2.172	[redacted]	1,123	Dominated
	Roclanda	[redacted]	0.000	[redacted]	Dominated	Dominated
	Dorzolamide-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide-brimonidine	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Latanoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
STC, excluding OHT patients (POAG patients included only)	Brinzolamide-timolol	-	-	-	-	-
	Netarsudil-latanoprost	[redacted]	0.000	[redacted]	Dominated	Dominated
	Dorzolamide-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide-brimonidine	[redacted]	0.000	[redacted]	342,699	347,712
	Brimonidine-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Latanoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
STC, excluding 8am data	Brinzolamide-timolol	-	-	-	-	-
	Netarsudil-latanoprost	[redacted]	0.000	[redacted]	Dominated	Dominated
	Dorzolamide-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide-brimonidine	[redacted]	0.000	[redacted]	4,855,215	Dominated
	Brimonidine-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Latanoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; MAIC– Matching-adjusted indirect comparison; QALYs – Quality-adjusted life years; STC – Simulated treatment comparison

B.3.10.3.10 Scenario analysis varying the AE probabilities

Scenario analyses were conducted varying the AE probabilities, to double and triple the base-case rates (Table 83).

Table 83: Scenario analyses varying the AE probabilities (incremental results vs. treatment with lowest total costs)

Multiplier applied to AE probabilities	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
Base-case rate doubled	Brinzolamide-timolol	-	-	-	-	-
	Dorzolamide-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide-brimonidine	[redacted]	0.000	[redacted]	178,685	159,073
	Roclanda	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brimonidine-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Latanoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
Base-case rate tripled	Brinzolamide-timolol	-	-	-	-	-
	Dorzolamide-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide-brimonidine	[redacted]	0.000	[redacted]	124,013	122,753
	Roclanda	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brimonidine-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Latanoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

B.3.10.3.11 Scenario analysis varying the QoL mapping method

A scenario analysis was conducted to apply a different mapping method for the conversion of SF-36 data to EQ-5D. For this scenario, the method from Rowen *et al.* was applied (Table 84).[115]

Table 84: Scenario analysis varying the QoL mapping method (incremental results vs. treatment with lowest total costs)

Methodology for mapping of QoL data	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
Rowen *et al.* 2009[115]	Brinzolamide-timolol	-	-	-	-	-
	Netarsudil-latanoprost	[redacted]	0.000	[redacted]	Dominated	Dominated
	Dorzolamide-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Brinzolamide- brimonidine	[redacted]	0.000	[redacted]	342,699	317,724
	Brimonidine-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Bimatoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Latanoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Travoprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated
	Tafluprost-timolol	[redacted]	0.000	[redacted]	Dominated	Dominated

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years; QoL – Quality-of-life

B.3.10.4 Summary of sensitivity analyses results

- In the probabilistic sensitivity analysis:
    - Probabilistic costs, LYs and QALYs were generally consistent with deterministic results. Netarsudil-latanoprost was associated with a total cost of [redacted] and mean total QALYs of [redacted]; mean probabilistic results are similar to the base case.
    - The ICEP shows that netarsudil-latanoprost is less costly than all FDC comparators and less effective however, the greatest incremental QALY difference between any treatment was only [redacted].
    - The majority of the iterations in the PSA were plotted in the south-west quadrant of the ICEP, demonstrating that netarsudil-latanoprost is generally less costly but less effective than the FDC comparators.
    - The CEAC demonstrates that brinzolamide-timolol has the highest probability of being the most cost-effective treatment at all WTP thresholds up to £100,000. Netarsudil-latanoprost is the second most cost-effective treatment at WTP thresholds of £0 - £25,000, after which point brinzolamide-brimonidine becomes the second most cost-effective treatment.
- In the deterministic sensitivity analysis:
    - Across the comparators, NMB results were most sensitive to total costs for each health state.
    - The largest difference in NMB observed for a single parameter is £874, indicating relative stability in the model results.
- In the scenario analyses, incremental costs were generally stable across all scenarios. Care should be taken when considering ICER changes as the small magnitude of incremental QALYs between the comparators creates an extreme sensitivity to the ICERs. The scenario with the most notable impact was for brinzolamide-timolol in the scenario analysis applying MAIC transition probabilities (change in incremental costs from [redacted]).

B.3.11 Subgroup analysis

Subgroup analysis was not performed as part of this submission.

B.3.12 Validation

The model has undergone internal and external validation. The model was developed internally by health economists and checked for accuracy by other analysts not involved in model development. External validation of the model was performed in multiple stages with multiple clinical experts. The stages are detailed below.

Prior to the development of the cost-effectiveness model, a protocol was developed to outline the key modelling assumptions and inputs to be implemented. The model protocol was put forward to a UK clinical expert with the following objectives:

- To ratify the appropriateness and suitability of the model structure.

- To ratify the appropriateness and suitability of the model health states and choice of outcomes.

At this stage (December 2022), the UK clinical expert influenced the structure of the model, stating that IOP is an appropriate efficacy measurement that is widely used in literature and guidelines, as well as being a good indicator for disease progression in POAG and OHT.[90] The clinical expert supported the proposed methodology to use health states based on percentage reduction in IOP, without absolute thresholds, to capture the wide range of patient IOP levels and needs.[90] The clinical expert also recommended usage of Canadian Agency for Drugs and Technologies in Health (CADTH) glaucoma guidelines to inform which percentage reduction thresholds should constitute the model health states.[94]

A second stage of clinical validation interviews involved the identification of data sources and confirmation of model inputs with three clinical experts.

- The validation of typical resource use for treatment of AEs, confirmation of concomitant treatment proportions, and confirmation of the relevance of the health states and outcomes for clinical meaningfulness.

A third stage of clinical validation (April 2023) involved the confirmation of which variables constituted treatment effect modifiers and prognostic variables for inclusion in the MAIC and STC comparisons, prior to conducting the analyses.

A fourth stage (May 2023) of clinical input involved the revalidation of inputs in the context of the results they generated, to assess whether they reflected what would be observed in clinical practice. This included estimates of the effectiveness and safety of netarsudil-latanoprost and comparators derived from the ITC, and the extrapolation of time on treatment.

- To ratify the appropriateness of key modelling assumptions surrounding patients in clinical practice (caregivers, treatment compliance, resource use, multipliers and concomitant treatments).

A fifth stage (June 2023) of clinical input involved validation of long-term clinical efficacy and management of AEs.

- To ratify the appropriateness of using the 'Average' extrapolation method for long-term clinical efficacy in the base case.

- The validation of typical management and resource use for treatment of AEs.

B.3.13 Interpretation and conclusions of economic evidence

The results from the deterministic base case analysis show that, over a lifetime time horizon, netarsudil-latanoprost is associated with lower average costs [redacted] when compared to all FDC comparators (except [redacted]), demonstrating that netarsudil-latanoprost is cost-saving vs. the FDC comparators. Over a lifetime time horizon, the maximum difference in QALYs between netarsudil-latanoprost and comparators is [redacted], indicating that the treatments considered have a similar effect on patient quality-of-life; this demonstrates that a cost-comparison approach is the most suitable incremental analysis method for this appraisal.

The mean results of the PSA were similar to the base case, confirming the deterministic results; netarsudil-latanoprost was associated with mean total costs of [redacted] and mean total

QALYs of [redacted]. The results from the PSA indicate that netarsudil-latanoprost is the second-cheapest treatment considered. Results for the OWSA and scenario analyses were also robust and demonstrated similar findings.

The availability of netarsudil-latanoprost as a new class of medication will allow treatment access to patients with intolerances or insufficient response to current IOP lowering medications. This will help lower the need for glaucoma surgery and reduce the risk of developing irreversible sight loss in patients with a previous unmet need, as well as decrease the direct and indirect costs associated.

Overall, this economic analysis shows that netarsudil-latanoprost may be considered a cost-saving and effective use of NHS resources for patients with POAG or OHT. It will provide an alternative treatment option in the management of these conditions, with a novel mechanism of action, for patients who are underserved by currently available therapies.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Netarsudil-latanoprost for previously treated open-angle glaucoma or ocular hypertension [ID1363]

Document B

Company evidence submission

March 2024

File name	Version	Contains confidential information	Date
ID1363_Netarsudil-latanoprost_Cost comparison_v2.0 updated ACIC mark up 04Jul24_Fullyredacted	**2.0**	**No**	**28 March 2024** **(ACIC mark up updated 04 July 2024)**

Summary of changes

Sections with updated information

- Section B.2.2Resource use assumptions: Resource use assumptions have now been updated since Technical Engagement following the assumption of equivalent efficacy across all treatments.
- Section B.3.10 Adverse reactionsto reflect EAG preferences of cost and resource use assumptions.
- Section B.3.11 Conclusions about comparable health benefits and safety: The NMA has been updated at Technical Engagement.
- Section B.4 Cost-comparison analysis: Market share calculations, as well as costs associated with acquisition, healthcare resource use, adverse events, wastage assumptions, and uncertainties in inputs have now been updated since Technical Engagement. Updated model base case, scenario analyses, and sensitivity analyses results are presented.

The sections detailed above were populated with updated information to ensure the cost-comparison model presents an analysis that is most relevant to the anticipated positioning of netarsudil-latanoprost, and to align with NICE's preferences where available. The remaining sections align with the original submission and the Technical Engagement response.

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) when a cost-comparison case is made as part of the single technology appraisal process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 100 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE health technology evaluation guidance development manual.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the footer with appropriate text. (To change the footer, double click over the footer text. Double click back in the main body text when you have finished.)

Contents

Tables and figures

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

Please see Section B.1.1 of the Company's original submission for details of the decision problem.

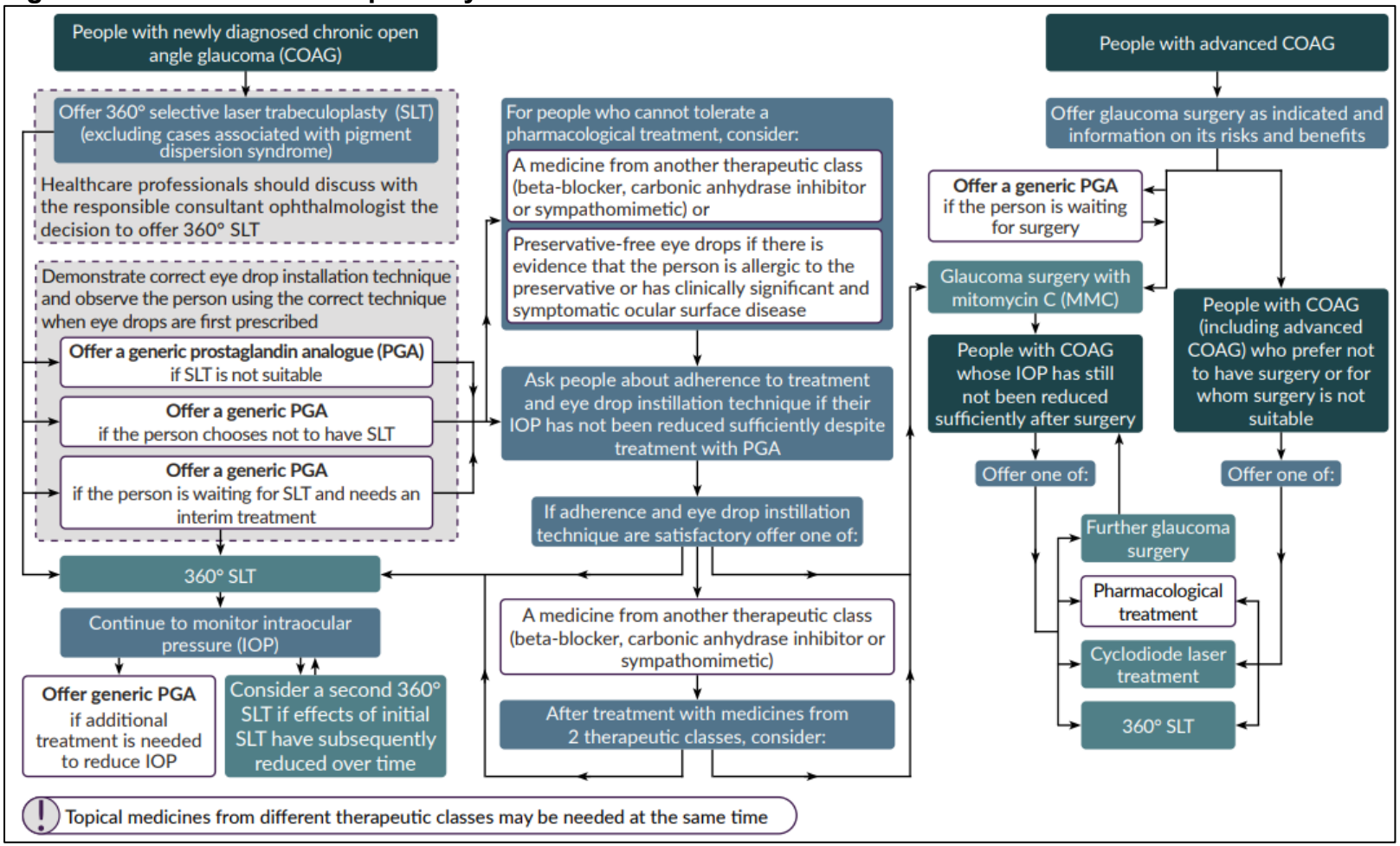
B.1.2 Description of the technology being evaluated

Please see Section B.1.2 of the Company's original submission for details of the decision problem.

B.1.3 Health condition and position of the technology in the treatment pathway

Details regarding the clinical pathway of care for primary open-angle glaucoma (POAG) and ocular hypertension (OHT) can be found in Section B.1.3 of Document B of the original submission. The current NICE treatment pathway for POAG and OHT are shown in Figure 1 and Figure 2. Netarsudil-latanoprost will fit into the existing treatment pathways at the point where patients show insufficient intraocular pressure (IOP) reduction following treatment with a generic PGA.

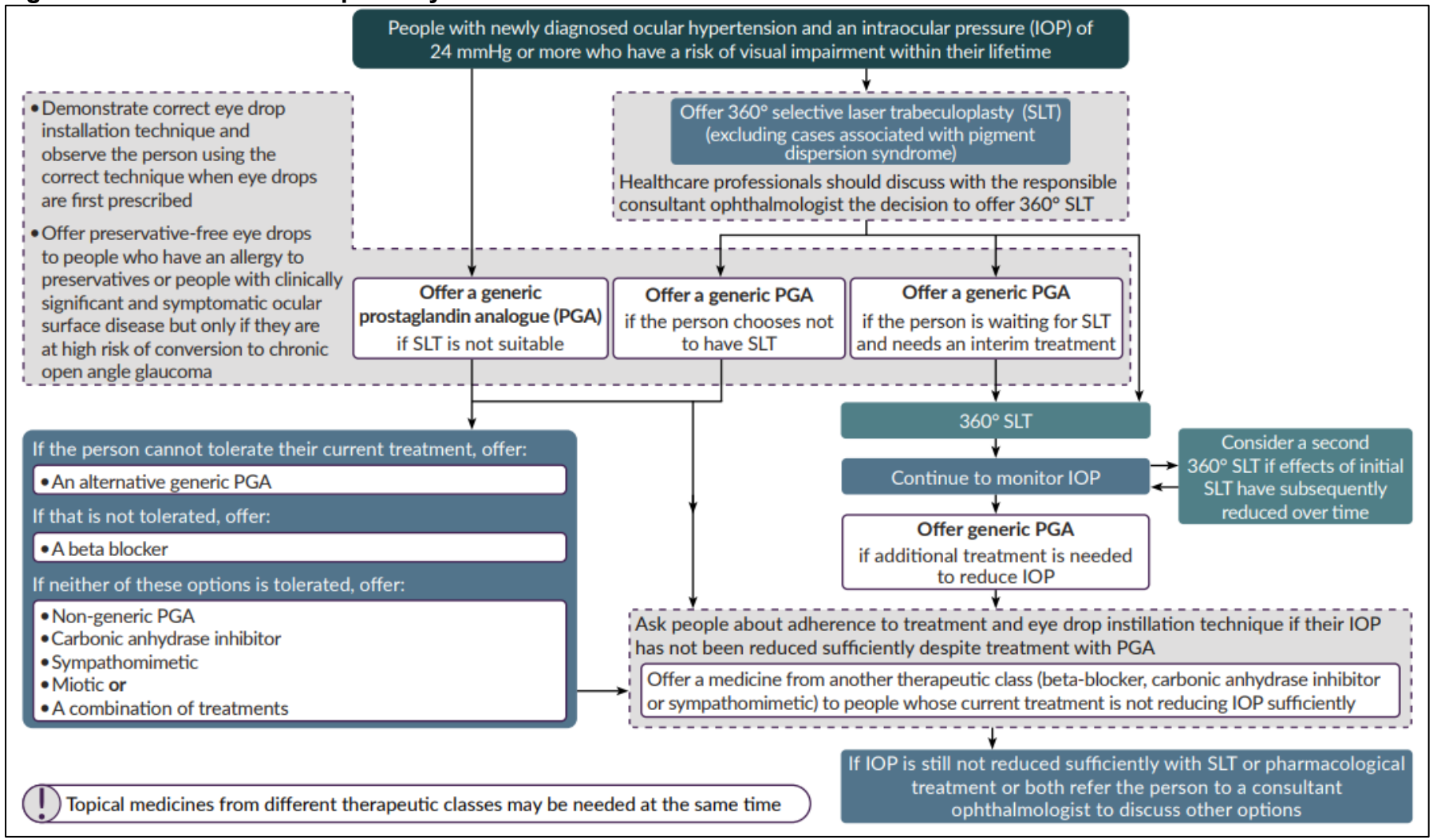
Figure 1: Current treatment pathway for POAG



Note: COAG is another term used for POAG.

Abbreviations: COAG – Chronic open-angle glaucoma; IOP – Intraocular pressure; MMC – Mitomycin C; PGA – Prostaglandin analogue; POAG – Primary open-angle glaucoma; SLT – Selective laser trabeculoplasty

Figure 2: Current treatment pathway for OHT



Abbreviations: IOP – Intraocular pressure; OHT – Ocular hypertension; PGA – Prostaglandin analogue; SLT – Selective laser trabeculoplasty

Whilst all branded and generic products are considered within this analysis to ensure transparency, the Company anticipate that netarsudil-latanoprost should be considered for POAG and OHT patients following a generic fixed-dose combination (FDC), or as a step up from monotherapy where a FDC containing beta blockers would not be appropriate. The key comparators relevant to netarsudil-latanoprost will therefore be the branded FDC products. This positioning is based upon clinical opinion of where netarsudil-latanoprost will be used in practice.

Netarsudil-latanoprost is the only PGA-containing FDC product that does not contain a beta blocker. This is important for patients who are not suitable for beta blockers due to contraindications, such as patients with respiratory diseases and underlying cardiovascular conditions. Netarsudil-latanoprost will provide a treatment option for these patients. Furthermore, netarsudil-latanoprost will also be a treatment for patients who are not suitable for beta blocker-containing ocular agents due to intolerance.

To provide context for treatment options available to POAG or OHT patients within a similar line of treatment, products included in the cost-comparison model are listed in Table 1. It is key to consider there are multiple categorisation approaches available:

- Broadly, products fall into active ingredient classes (presented in Table 1 as “Active ingredient (FDC)”)
- From this, products can be grouped into their Virtual Medicinal Product (VMP) category (presented in Table 1 as “Treatment - naming per DM+D (VMP)”)
- Final differentiation can be established through products grouping into Actual Medicinal Product (AMP) groupings (presented in Table 1 as “Treatment - naming per DM+D (AMP)”)

While some products are composed of the same FDC of active ingredients, products should be considered distinct as they can differ by their preservative-free status, unit dose, or as generic or branded versions of the same product. In Table 1, grouping by VMP category can be used to help understand if a branded product has a direct generic comparator – in several cases, some branded products have no generic alternative.

Table 1: Products included in the cost-comparison analysis

Active ingredient (FDC)	Treatment - naming per DM+D (VMP)	Treatment - naming per DM+D (AMP)
Netarsudil & Latanoprost	Latanoprost 50micrograms/ml / Netarsudil 200micrograms/ml	Roclanda 50micrograms/ml + 200micrograms/ml eye drops
Brinzolamide & Timolol	Brinzolamide 10mg/ml / Timolol 5mg/ml eye drops	Azarga 10mg/ml / 5mg/ml eye drops
		Brinzolamide 10mg/ml / Timolol 5mg/ml eye drops
Dorzolamide & Timolol	Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops 0.2ml unit dose preservative free	Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops 0.2ml unit dose preservative free
		Cosopt 20mg/ml / 5mg/ml eye drops 0.2ml unit dose preservative free
	Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops	Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops
		Cosopt 20mg/ml / 5mg/ml eye drops

Active ingredient (FDC)	Treatment - naming per DM+D (VMP)	Treatment - naming per DM+D (AMP)
	Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops preservative free	Cosopt iMulti 20mg/ml / 5mg/ml eye drops preservative free
		Eylamdo 20mg/ml / 5mg/ml eye drops
		Vizidor Duo 20mg/ml / 5mg/ml eye drops
Latanoprost & Timolol	Latanoprost 50micrograms/ml / Timolol 5mg/ml eye drops	Latanoprost 50micrograms/ml / Timolol 5mg/ml eye drops
		Medox 50micrograms/ml / 5mg/ml eye drops
		Xalacom eye drops
	Latanoprost 50micrograms/ml / Timolol 5mg/ml eye drops 0.2ml unit dose preservative free	Fixapost 50micrograms/ml / 5mg/ml eye drops 0.2ml unit dose
Tafluprost & Timolol	Tafluprost 15micrograms/ml / Timolol 5mg/ml eye drops 0.3ml unit dose preservative free	Taptiqom 15micrograms/ml / 5mg/ml eye drops 0.3ml unit dose

Active ingredient (FDC)	Treatment - naming per DM+D (VMP)	Treatment - naming per DM+D (AMP)
Bimatoprost & Timolol	Bimatoprost 300micrograms/ml / Timolol 5mg/ml eye drops	Bimatoprost 300micrograms/ml / Timolol 5mg/ml eye drops
		Ganfort 0.3mg/ml / 5mg/ml eye drops
	Bimatoprost 300micrograms/ml / Timolol 5mg/ml eye drops preservative free	Eyzeetan 0.3mg/ml / 5mg/ml eye drops preservative free
	Bimatoprost 300micrograms/ml / Timolol 5mg/ml eye drops 0.4ml unit dose preservative free	Ganfort 0.3mg/ml / 5mg/ml eye drops 0.4ml unit dose
Travoprost & Timolol	Travoprost 40micrograms/ml / Timolol 5mg/ml eye drops	Travoprost 40micrograms/ml / Timolol 5mg/ml eye drops
		DuoTrav 40micrograms/ml / 5mg/ml eye drops
Brinzolamide & Brimonidine	Brinzolamide 10mg/ml / Brimonidine 2mg/ml eye drops	Simbrinza 10mg/ml / 2mg/ml eye drops

Active ingredient (FDC)	Treatment - naming per DM+D (VMP)	Treatment - naming per DM+D (AMP)
Brimonidine & Timolol	Brimonidine 2mg/ml / Timolol 5mg/ml eye drops	Combigan eye drops (priced by 3*5ml pack)
		Combigan eye drops (priced by 1*5ml pack)

Abbreviations: DM+D – Dictionary of medicines and devices

The Company are aware that within AMP categories, there could be further differentiation to account for different suppliers and pack sizes – however to avoid presentation of a significant number of comparators, where a product presents an equal cost per drop (which accounts for factors such as drop size, shelf life, and container size). Note that for Brimonidine 2mg/ml / Timolol 5mg/ml eye drops, while the only AMP product is Combigan, Combigan can be sold in packs of one or three, with price variation for buying a greater number of packs – these products therefore have been differentiated due to a differing cost per drop.

Further details on grouping products are given in Section B.4 Cost-comparison analysis.

B.1.4 Equality considerations

Please see Section B.1.4 of the Company's original submission for details of the decision problem.

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

Following results from the network meta-analysis (NMA) conducted during the Technical Engagement stage of the original submission, summarised in Section B.3.9

Indirect and mixed treatment comparisons, netarsudil-latanoprost showed no significant difference in treatment effects when compared with all other comparators, indicating that the treatments have similar efficacy. Following agreement with the NICE Committee, as there is no expected difference in clinical outcomes and measures between netarsudil-latanoprost and its comparators, clinical outcomes and measures would not be key drivers of cost-effectiveness in the analysis and can therefore be disregarded.

That said, while the efficacy of treatments is similar, the adverse events (AE) experienced by patients are not considered equal between treatments. The probability of AEs associated with each treatment aligns with Table 46 of Section B.3.3.3 in Document B of the original submission. The different AE rates impact the total costs and subsequent cost-minimisation ranking of each treatment and therefore must be included in this analysis. The costs and resource use associated with AEs are further detailed in Section B.4 Cost-comparison analysis.

B.2.2 Resource use assumptions

The resource use for netarsudil-latanoprost and comparators is presented in this analysis as drug acquisition costs. Drivers of acquisition costs are based mostly on their list price, but also considers wastage and product shelf life once opened as this impacts the quantity of units required per model cycle. Drop size is used in wastage calculations, subsequently impact products acquisition cost per cycle. Further details on the wastage assumptions and calculations are described with acquisition costs in Section B.4 Cost-comparison analysis.

Additionally, due to treatment efficacy being assumed equal across comparators, resource use associated with disease management is therefore also assumed to be

equal regardless of treatment. The resource use associated with AEs were applied to products based on the FDC that the product consisted of and was applied with varying assumptions based on the adverse event severity. These assumptions align with the External Assessment Group (EAG)'s preferences and are detailed further in Section B.4 Cost-comparison analysis.

B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

To ensure relevant and robust clinical effectiveness evidence was used to inform the analysis, literature searches were conducted or updated at each stage of the submission. Beyond that described in Section B.2 of Document B from the original submission, a key element to note is that of the systematic literature review (SLR) conducted to inform the NMA undertaken as part of the response at the Technical Engagement stage, which is detailed in the response to Issue 1 of the Technical Engagement response form.

B.3.2 List of relevant clinical effectiveness evidence

The evidence base for netarsudil-latanoprost is provided in the MERCURY 3 trial, as described in Section B.2.2 of Document B from the original submission.

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

The MERCURY 3 trial methodology is detailed in Section B.2.2 of Document B from the original submission.

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The statistical analyses conducted for the MERCURY 3 trial is detailed in Section B.2.2 of Document B from the original submission.

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

A complete quality assessment for the MERCURY 3 trial is available in Appendix D of Document B of the original submission.

B.3.6 Clinical effectiveness results of the relevant studies

Clinical effectiveness results of the MERCURY 3 trial are available in Section B.2.6 of Document B from the original submission, while results of the remaining trials can be found in the Appendix of the Technical Engagement response form.

B.3.7 Subgroup analysis

As within the original submission, no subgroup analyses were conducted at this stage as there were no subgroups of interest.

B.3.8 Meta-analysis

A meta-analysis was not conducted, as the only relevant clinical trial identified for netarsudil-latanoprost relevant to this submission is MERCURY 3.

B.3.9 Indirect and mixed treatment comparisons

See Appendix D for full details of the methodology for the indirect comparison or mixed treatment comparison.

Details of the NMA conducted can be found in the response to Issue 1 of the Technical Engagement response form. While the NMA was conducted for the previous model, in line with the assumption of equivalent efficacy across the comparators, the NMA values have not been applied in the current model.

Uncertainties in the indirect and mixed treatment comparisons

Details regarding uncertainties in the NMA conducted can be found in the response to Issue 1 of the Technical Engagement response form.

B.3.10 Adverse reactions

Details of adverse reactions observed in the MERCURY 3 trial can be found in Section B.2.10 of Document B from the original submission. Of note, a different AE cost and resource use approach was used in comparison with that from the original submission, and this is detailed in the response for Issue 6 of the Technical Engagement response form. It was assumed that mild AEs would not incur any costs, moderate AEs would use EAG preferred resource use assumptions, while severe AEs would use resource use assumptions from the original submission. These assumptions were then applied

to the AEs by severity as was reported in the MERCURY 3 trial data to obtain the total cost per AE occurrence. This was to align AE assumptions to that requested by the EAG. Table 2 present the approach taken, demonstrating the cost differences between moderate and severe severities of each AE.

Further details for the approach can be found in Section B.4 Cost-comparison analysis.

Table 2: Adverse cost calculations by severity

Adverse event	Moderate AE cost	Severe AE cost	Weighted percent of AE as moderate	Weighted percent of AE as severe	Cost per AE - weighted by severity
Conjunctival hyperaemia	0.00	212.96	[redacted]	[redacted]	[redacted]
Cornea verticillate	0.00	141.97	[redacted]	[redacted]	[redacted]
Conjunctival haemorrhage	70.99	283.95	[redacted]	[redacted]	[redacted]
Eye pruritis	70.99	212.96	[redacted]	[redacted]	[redacted]
Punctate keratitis	70.99	354.93	[redacted]	[redacted]	[redacted]
Conjunctivitis allergic	141.97	283.95	[redacted]	[redacted]	[redacted]
Viral upper respiratory tract infection	0.00	42.00	[redacted]	[redacted]	[redacted]
Hypertension	0.00	537.86	[redacted]	[redacted]	[redacted]
Abnormal vision	141.97	283.95	[redacted]	[redacted]	[redacted]
Blurred vision	141.97	283.95	[redacted]	[redacted]	[redacted]
Change of eyelashes	0.00	0.00	[redacted]	[redacted]	[redacted]
Conjunctival blanching	0.00	0.00	[redacted]	[redacted]	[redacted]
Dry eye	0.00	0.69	[redacted]	[redacted]	[redacted]
Eye allergy	141.97	283.95	[redacted]	[redacted]	[redacted]
Eye irritation	0.00	0.69	[redacted]	[redacted]	[redacted]
Eye pain	141.97	283.95	[redacted]	[redacted]	[redacted]
Eyelash discolouration	0.00	0.00	[redacted]	[redacted]	[redacted]
Foreign body sensation in eyes	141.97	283.95	[redacted]	[redacted]	[redacted]

Adverse event	Moderate AE cost	Severe AE cost	Weighted percent of AE as moderate	Weighted percent of AE as severe	Cost per AE - weighted by severity
Headache	0.00	2.44	[redacted]	[redacted]	[redacted]
Ocular discomfort	70.99	283.95	[redacted]	[redacted]	[redacted]
Ocular hyperaemia	0.00	0.00	[redacted]	[redacted]	[redacted]
Photophobia	70.99	283.95	[redacted]	[redacted]	[redacted]
Visual disturbance	70.99	283.95	[redacted]	[redacted]	[redacted]

Abbreviations: AE – Adverse event

B.3.11 Conclusions about comparable health benefits and safety

Prior to the conclusion that all treatments should be considered with equal efficacy, multiple renditions of an NMA were undertaken. Of note to this stage of the submission, an updated NMA using a robust connected evidence network was submitted in response to the EAG clarification questions, and the methodology and results are detailed in the response to Issue 1 of the Technical Engagement response form. The NMA network of evidence consisted of 10 randomised controlled trials (RCTs) deemed feasible to assess the percentage change in diurnal IOP from baseline. The NMA results showed that there was no significant difference in treatment effects when netarsudil-latanoprost was compared with all other comparators, indicating that the treatments have similar efficacy. The NMA results of the base-case random effects model analysis from the Technical Engagement response is as shown in Figure 3. Similar results can be observed in the scenario analysis using the fixed effect model as shown in Figure 4.

This was consistent with the base-case analysis provided during the EAG clarification questions, where no results demonstrated statistical significance. The NMA utilised a connected evidence network consisting of nine RCTs to assess the same endpoint. Further details of the methodology and results of this NMA can be found in A8 of the EAG clarification questions.

Figure 3: Forest plot – percentage change in diurnal IOP from baseline (random effects model)

Abbreviations: IOP – Intraocular pressure; SD – Standard deviation

Figure 4: Forest plot – percentage change in diurnal IOP from baseline (fixed effects model)

Abbreviations: IOP – Intraocular pressure; SD – Standard deviation

B.3.12 Ongoing studies

There are no ongoing studies that will provide additional evidence in the next 12 months for the indication being appraised. Of note, netarsudil-latanoprost is currently being used at Moorfields Eye Hospital for the treatment of open-angle glaucoma and OHT following local guidelines, and has been approved for use since August 2023.[1]

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Netarsudil-latanoprost will be provided in secondary care; treatment with netarsudil-latanoprost should be initiated by an ophthalmologist or a healthcare professional qualified in ophthalmology. This aligns with the setting of care for the FDC comparators listed in the NICE scope.

As shown by market share data, some branded products have generic competitors since losing patent protection. However, the data illustrates that after the initial drop in market share of branded products due to generics, branded products adopt a stable position, retaining a significant volume of usage. As such, the model has been updated to provide a direct comparison to each individual product for transparency, avoiding grouping of comparator combinations. This approach accounts for the generally larger difference in costs between branded and generic products, as using an average cost across all products in the same FDC class may provide an inaccurate presentation of costs. Instead, products with the same AMP definition (meaning they have equal preservative-free status, and branded or generic status), as well as an equal price per drop, were grouped together for calculations.

Where generic products have been included, the listed drug tariff price has been applied. Where branded products have been included, the listed NHS indicative price has been applied to represent that in real-world practice doctors continue to specifically prescribe some brand written prescriptions as opposed to generically written prescriptions for all, as shown by the market share data. Additionally, the Dictionary of medicines and devices (DM+D) naming convention, which is used to identify interchangeable medicines when a generically written prescription is given, was also used to group products. This allows for cost per drop differences between comparable products to be seen, and highlights cost differences between different classes of products, products with different preservative-free status, as well as branded against generic products.

A description of netarsudil-latanoprost is provided in Section B.1.2 (Table 2) of the original submission, including the method of administration and dosing and additional

tests or investigations. The frequency of administration of netarsudil-latanoprost is aligned to the drug composition of the FDC comparators (bimatoprost-timolol, latanoprost-timolol, tafluprost-timolol and travoprost-timolol) – one drop in the affected eye(s), once daily. For the remaining drug compositions (brinzolamide-timolol, dorzolamide-timolol, brinzolamide-brimonidine and brimonidine-timolol), treatment is administered as one drop twice daily. All products are self-administered negating the requirement of any resource use to administer treatment.

B.4.2 Cost-comparison analysis inputs and assumptions

Features of the cost-comparison analysis

The time horizon used in the cost-minimisation model base case is 12 months, as aligned with the rationale presented in the response to Issue 2 of the Technical Engagement response form. As the time horizon is 12 months, discounting is not applicable.

The selection of the time horizon was made based on time on treatment, allowing for discontinuation to be excluded. A time horizon of 12 months was considered suitable given the heterogeneity of median time to discontinuation across all the comparators, ranging from 12 to 21 cycles, and netarsudil-latanoprost at 15 cycles (see Table 3).

Table 3: Time on treatment per product FDC composition

Comparator class	Comparators	Cycle at which 0.50 discontinuation	Source assumption
RKI+PGA	Netarsudil-latanoprost	15	-
CAI+BB	Dorzolamide and timolol	21	
CAI+BB	Brinzolamide and timolol	21	Assumed equal to dorzolamide and timolol
CAI+SYMP	Brinzolamide and brimonidine	19	-
SYMP+BB	Brimonidine and timolol	12	-
PGA+BB	Bimatoprost and timolol	102	-
PGA+BB	Latanoprost and timolol	102	Assumed equal to bimatoprost and timolol
PGA+BB	Tafluprost and timolol	102	
PGA+BB	Travoprost and Timolol	102	

Abbreviations: BB – Beta blocker; CAI - Carbonic anhydrase inhibitor; PGA – Prostaglandin analogue; RKI – Rho kinase inhibitor; SYMP - Sympathomimetic

This summary data is exclusive of data shared in the original submission for bimatoprost and timolol's time on treatment – this product presents a median time on treatment of 102 months, significantly different to all other data in the market. The clinical study report states that those eligible for treatment must not be treatment naïve nor present any sensitivity to investigational formulations. This means that only those who tolerate bimatoprost and timolol are included in MERCURY 3 – an unfair representation of the POAG/OHT population.

As noted at Technical Engagement, a 12-month time horizon reduces uncertainty as longer-term time horizons are dependent on estimates, extrapolations, and assumptions of longer-term efficacy, quality of life (QoL), costs, and the treatment pathway for discontinuing patients, for which data is limited. Furthermore, the nature of netarsudil-latanoprost and its indication, with many treatment options and frequent product rotation in the patient journey, is suitable to justify a short time horizon. The lack of data available to link between short- and long-term progression of the disease, i.e., linking IOP to glaucoma severity, also suggest a shorter time horizon is more suitable, to avoid unrealistic assumptions and extrapolations. The one-year time horizon reflects a patient's short-term treatment journey instead of representing a patient's full time on treatment.

Though not included in model calculations, market share is calculated for presentation purposes to aid the user in the assessment of appropriate comparison across products. To product these supportive values, unit sales data from 2022 was first obtained for each product. Products were then grouped together if they contained the same active ingredient and had the same price per drop (or per unit where more appropriate). Parallel Import (PI) products were included in market share calculations as an addition to their respective products. Following that, each product's overall percentage market share was calculated to determine the product's market share as compared with all other products included in the analysis. No extrapolations were carried out for market share data from 2022 to align with the last observation carried forward approach as per NICE's feedback.

Additionally, to help understand the dynamics within DM+D VMP groupings, the market share split between products to demonstrate that despite the availability of generic FDCs, branded FDCs remain in use.

Market shares should be assessed alongside overall cost-minimisation results to ensure netarsudil-latanoprost can be compared against the branded FDC products within the same line of treatment.

Intervention and comparators' acquisition costs

The list price of netarsudil-latanoprost is due to be set to a cost per pack of £10.00. In addition, this aligns the price of netarsudil-latanoprost more closely with Simbrinza (brinzolamide-brimonidine), Ganfort unit dose (bimatoprost-timolol), Eyzeetan (bimatoprost-timolol), Fixapost (latanoprost-timolol), and Taptiqom (tafluprost-timolol), which are the only other branded products with no generic alternatives.

Table 4 to Table 7 below shows the acquisition costs of netarsudil-latanoprost and the remaining 23 comparators. The costs detailed and used in the analysis account for wastage. The number of drops available per container for each product was first calculated by dividing the container size by the drop size. For products where a unit dose was not used, a drop size of 0.035ml was assumed.

Previously, a drop size of 0.05ml was assumed for each comparator besides netarsudil-latanoprost in the analysis at Technical Engagement. However, the Company has data on file to support the use of a 0.035ml drop size for netarsudil-latanoprost.[2] A drop size of 0.035ml was used to calculate a fill volume of 2.5ml listed in the summary of product characteristics. This volume would provide more than enough drops for one drop per affected eye per day over a month. The drop size for all comparators were therefore adjusted to 0.035ml as a data-driven assumption.

The number of drops needed per cycle for each product was divided by the drops available per container to calculate the percentage of a pack of product used per cycle. By comparison of the percentage of a pack used per cycle against the product shelf life, it was determined if wastage due to expiration for a product would occur. In the base case, it was assumed that if a product is not fully utilised within a model cycle, instead of disregarding carry over between cycles, a patient would instead receive a

new product each time the product expires. A scenario analysis was also conducted, where it was assumed that no product could be transferred to the next cycle, thus a new pack of product would be started every month.

Table 4: Acquisition costs of the intervention and comparator technologies (1/4)

	Roclanda (netarsudil-latanoprost)	Azarga (brinzolamide-timolol)	Generic brinzolamide-timolol	Generic dorzolamide-timolol, 60.2ml	Generic dorzolamide-timolol, 5ml	Cosopt, single dose (dorzolamide-timolol), 5ml
Pharmaceutical formulation	Netarsudil-latanoprost	Brinzolamide-timolol	Brinzolamide-timolol	Dorzolamide-timolol	Dorzolamide-timolol	Dorzolamide-timolol
(Anticipated) care setting	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx
Acquisition cost per month (excluding VAT, £)	9.32 (NHS indicative price)	10.30 (NHS indicative price)	2.96 (Drug tariff price)	17.86 (Drug tariff price)	1.58 (Drug tariff price)	9.37 (NHS indicative price)
Method of administration	Topically in the eye	Topically in the eye	Topically in the eye	Topically in the eye	Topically in the eye	Topically in the eye
Dosing frequency per day	Once daily, per eye	Twice daily, per eye	Twice daily, per eye	Twice daily, per eye (one UD does two eyes)	Twice daily, per eye	Twice daily, per eye
Price per pack (£)	10.00	11.05	3.17	17.86	1.70	10.05
Number of doses per pack*	50.00	100.00	100.00	UD	100.00	100.00
Number of doses per month	60.88	121.75	121.75	60.88	121.75	121.75

* Number of doses per pack was calculated by dividing each product's container size by the drop size. A conversion factor of 0.05ml per drop was assumed.

Abbreviations: Rx – Medical prescription; UD – Unit dose

Table 5: Acquisition costs of the intervention and comparator technologies (2/4)

	Cosopt, single dose dorzolamide-timolol, 60.2ml	Cosopt, multi dose dorzolamide-timolol, 10ml	Eylamdo (dorzolamide-timolol)	Vizidor (dorzolamide-timolol)	Generic latanoprost-timolol	Fixapost (latanoprost-timolol)
Pharmaceutical formulation	Dorzolamide-timolol	Dorzolamide-timolol	Dorzolamide-timolol	Dorzolamide-timolol	Latanoprost-timolol	Latanoprost-timolol
(Anticipated) care setting	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx
Acquisition cost per month (excluding VAT, £) *	28.59 (NHS indicative price)	14.00 (NHS indicative price)	7.58 (NHS indicative price)	7.59 (NHS indicative price)	4.85 (Drug tariff price)	13.49 (NHS indicative price)
Method of administration	Topically in the eye	Topically in the eye	Topically in the eye	Topically in the eye	Topically in the eye	Topically in the eye
Dosing frequency per day	Twice daily, per eye (one UD does two eyes)	Twice daily, per eye	Twice daily, per eye	Twice daily, per eye	Once daily, per eye	Once daily, per eye (one UD does two eyes)
Price per pack (£)	28.59	28.00	8.13	8.14	5.20	13.49
Number of doses per pack*	60.00	10.00	5.00	5.00	2.50	30.00
Number of doses per month	60.88	121.75	121.75	121.75	60.88	30.44

* Number of doses per pack was calculated by dividing each product's container size by the drop size. A conversion factor of 0.05ml per drop was assumed.

Abbreviations: Rx – Medical prescription; UD – Unit dose

Table 6: Acquisition costs of the intervention and comparator technologies (3/4)

	Medox (latanoprost-timolol)	Xalacom (latanoprost-timolol)	Taptiqom (tafluprost-timolol)	Generic bimatoprost-timolol	Eyzeetan (bimatoprost-timolol)	Ganfort drops (bimatoprost-timolol)
Pharmaceutical formulation	Latanoprost-timolol	Latanoprost-timolol	Tafluprost-timolol	Bimatoprost-timolol	Bimatoprost-timolol	Bimatoprost-timolol
(Anticipated) care setting	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx
Acquisition cost per month (excluding VAT, £) *	13.05 (NHS indicative price)	13.35 (NHS indicative price)	14.50 (NHS indicative price)	11.19 (Drug tariff price)	11.19 (NHS indicative price)	14.16 (NHS indicative price)
Method of administration	Topically in the eye	Topically in the eye	Topically in the eye	Topically in the eye	Topically in the eye	Topically in the eye
Dosing frequency per day	Once daily, per eye	Once daily, per eye	Once daily, per eye (one UD does two eyes)	Once daily, per eye	Once daily, per eye	Once daily, per eye
Price per pack (£)	14.00	14.32	14.50	14.16	14.16	14.16
Number of doses per pack*	2.50	2.50	30.00	3.00	3.00	3.00
Number of doses per month	60.88	60.88	30.44	60.88	60.88	60.88

* Number of doses per pack was calculated by dividing each product's container size by the drop size. A conversion factor of 0.05ml per drop was assumed.

Abbreviations: Rx – Medical prescription; UD – Unit dose

Table 7: Acquisition costs of the intervention and comparator technologies (4/4)

	Ganfort single dose units (bimatoprost-timolol)	Generic travoprost-timolol	Duotrav (travoprost-timolol)	Simbrinza (brinzolamide-brimonidine)	Combigan (brimonidine-timolol), 3*5ml	Combigan (brimonidine-timolol), 1*5ml
Pharmaceutical formulation	Bimatoprost-timolol	Travoprost-timolol	Travoprost-timolol	Brinzolamide-brimonidine	Brimonidine-timolol	Brimonidine-timolol
(Anticipated) care setting	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx	Secondary care for initiation of Rx, primary care for continuation of Rx
Acquisition cost per month (excluding VAT, £) *	14.18 (NHS indicative price)	4.20 (Drug tariff price)	13.01 (NHS indicative price)	8.61 (NHS indicative price)	9.00 (NHS indicative price)	9.32 (NHS indicative price)
Method of administration	Topically in the eye	Topically in the eye	Topically in the eye	Topically in the eye	Topically in the eye	Topically in the eye
Dosing frequency per day	Once daily, per eye (one UD does two eyes)	Once daily, per eye	Once daily, per eye	Twice daily, per eye	Twice daily, per eye	Twice daily, per eye
Price per pack (£)	17.94	4.51	13.95	9.23	27.00	10.00
Number of doses per pack*	30.00	2.50	2.50	5.00	15.00	5.00
Number of doses per month	30.44	60.88	60.88	121.75	121.75	121.75

* Number of doses per pack was calculated by dividing each product's container size by the drop size. A conversion factor of 0.05ml per drop was assumed.

Abbreviations: Rx – Medical prescription; UD – Unit dose

Table 8: Costs of the intervention and comparator technologies per cycle of treatment (1/4)

	Roclanda (netarsudil-latanoprost)	Azarga (brinzolamide-timolol)	Generic brinzolamide-timolol	Generic dorzolamide-timolol, 60.2ml	Generic dorzolamide-timolol, 5ml	Cosopt, single dose (dorzolamide-timolol), 5ml
Acquisition costs						
Unit cost						
Cost (£)	0.20	2.21	0.63	0.30	0.34	2.01
Source reference	Santen	BNF[3]	BNF[3]	BNF[4]	BNF[4]	BNF[4]
Units per course of treatment						
Number of units	50.00	5.00	5.00	60.00	5.00	5.00
Source reference	Santen	SmPC[5]	SmPC[6]	SmPC[7]	SmPC[8]	SmPC[9]
Total cost of acquisition						
Per course of treatment	9.32	10.30	2.96	17.86	1.58	9.37

Table 9: Costs of the intervention and comparator technologies per cycle of treatment (2/4)

	Cosopt, single dose (dorzolamide-timolol), 60.2ml	Cosopt, multi dose 10ml (dorzolamide-timolol)	Eylamdo (dorzolamide-timolol)	Vizidor (dorzolamide-timolol)	Generic (latanoprost-timolol)	Fixapost (latanoprost-timolol)
Acquisition costs						
Unit cost						
Cost (£), price year	0.48	2.80	1.63	1.63	2.08	0.45
Source reference	BNF[4]	BNF[4]	BNF[4]	BNF[4]	BNF[10]	BNF[10]
Units per course of treatment						
Number of units	60.00	10.00	5.00	5.00	2.50	30.00
Source reference	SmPC[9]	SmPC[11]	SmPC[12]	SmPC[13]	SmPC[14]	SmPC[15]
Total cost of acquisition						
Per course of treatment	28.59	14.00	7.58	7.59	4.85	13.49

Table 10: Costs of the intervention and comparator technologies per cycle of treatment (3/4)

	Medox (latanoprost-timolol)	Xalacom (latanoprost-timolol)	Taptiqom (tafluprost-timolol)	Generic bimatoprost-timolol	Eyzeetan (bimatoprost-timolol)	Ganfort drops (bimatoprost-timolol)
Acquisition costs						
Unit cost						
Cost (£), price year	5.60	5.73	0.48	4.72	4.72	4.72
Source reference	BNF[10]	BNF[10]	BNF[16]	BNF[17]	BNF[17]	BNF[17]
Units per course of treatment						
Number of units	2.50	2.50	30.00	3.00	3.00	3.00
Source reference	SmPC	SmPC[18]	SmPC[19]	SmPC[20]	SmPC[21]	SmPC[22]
Total cost of acquisition						
Per course of treatment	13.05	13.35	14.50	11.19	11.19	14.16

Table 11: Costs of the intervention and comparator technologies per cycle of treatment (4/4)

	Ganfort single dose units (bimatoprost-timolol)	Generic travoprost-timolol	Duotrav (travoprost-timolol)	Simbrinza (brinzolamide-brimonidine)	Combigan (brimonidine-timolol), 3*5ml	Combigan (brimonidine-timolol), 5ml
Acquisition costs						
Unit cost						
Cost (£), price year	0.60	1.80	5.58	1.85	1.80	2.00
Source reference	BNF[17]	BNF[23]	BNF[23]	BNF[24]	BNF[25]	BNF[25]
Units per course of treatment						
Number of units	30.00	2.50	2.50	5.00	15.00	5.00
Source reference	SmPC[26]	SmPC[27]	SmPC[28]	SmPC[29]	SmPC[30]	SmPC[30]
Total cost of acquisition						
Per course of treatment	14.18	4.20	13.01	8.61	9.00	9.32

Intervention and comparators' healthcare resource use and associated costs

Resource use, implicitly associated with disease management, is therefore assumed equal across all comparators in this model, due to the assumption of equivalent efficacy across all comparators. Consequently, no healthcare resource use costs are considered in the base case of the current model.

Administration costs and disease management costs are aligned with the respective costs and resource use presented in the model submitted as part of the Technical Engagement response. Healthcare resource use and costs applied for all technologies are presented in Table 12.

Table 12: Healthcare resource use and costs

Resource	Unit cost (£)	Health state	Resource use per cycle	Total cost per month (£)
GP visits	42.00	<20% reduction in IOP	0.0156	0.66
		20%-30% reduction in IOP	0.0153	0.64
		>30% reduction in IOP	0.0149	0.63
A&E attendance	143.74	<20% reduction in IOP	0.0115	1.65
		20%-30% reduction in IOP	0.0112	1.61
		>30% reduction in IOP	0.0109	1.57
Inpatient appointments	98.42	<20% reduction in IOP	0.000	0.00
		20%-30% reduction in IOP	0.000	0.00
		>30% reduction in IOP	0.000	0.00
Outpatient appointments	235.00	<20% reduction in IOP	0.000	0.00
		20%-30% reduction in IOP	0.000	0.00
		>30% reduction in IOP	0.000	0.00
Ophthalmologist appointments	141.97	<20% reduction in IOP	0.2342	33.25
		20%-30% reduction in IOP	0.2286	32.46
		>30% reduction in IOP	0.2231	31.67
Optometrist visit	57.54	<20% reduction in IOP	0.0699	4.02
		20%-30% reduction in IOP	0.0682	3.93
		>30% reduction in IOP	0.0666	3.83

Adverse reaction unit costs and resource use

Adverse event costs and resource use are aligned with that presented in the response to Issue 6 of the Technical Engagement response form. To account for the structural changes made to the model at this stage of the submission process, it has been assumed that the existing data available for adverse event frequencies can be applied to all comparators. Table 13 presents the link between the AMP named product, and the data used from the original submission to reflect AE frequency.

Table 13: Aligning products with available adverse event data

Treatment - naming per DM+D (AMP)	Product link to available FDC category
Roclanda 50micrograms/ml + 200micrograms/ml eye drops	Roclanda
Azarga 10mg/ml / 5mg/ml eye drops	Brinzolamide and timolol
Brinzolamide 10mg/ml / Timolol 5mg/ml eye drops	Brinzolamide and timolol
Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops 0.2ml unit dose preservative free	Dorzolamide and timolol
Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops	Dorzolamide and timolol
Cosopt 20mg/ml / 5mg/ml eye drops	Dorzolamide and timolol
Cosopt 20mg/ml / 5mg/ml eye drops 0.2ml unit dose preservative free	Dorzolamide and timolol
Cosopt iMulti 20mg/ml / 5mg/ml eye drops preservative free	Dorzolamide and timolol
Eylamdo 20mg/ml / 5mg/ml eye drops	Dorzolamide and timolol
Vizidor Duo 20mg/ml / 5mg/ml eye drops	Dorzolamide and timolol
Latanoprost 50micrograms/ml / Timolol 5mg/ml eye drops	Latanoprost and timolol
Fixapost 50micrograms/ml / 5mg/ml eye drops 0.2ml unit dose	Latanoprost and timolol
Medox 50micrograms/ml / 5mg/ml eye drops	Latanoprost and timolol
Xalacom eye drops	Latanoprost and timolol
Taptiqom 15micrograms/ml / 5mg/ml eye drops 0.3ml unit dose	Tafluprost and timolol
Bimatoprost 300micrograms/ml / Timolol 5mg/ml eye drops	Bimatoprost and timolol
Eyzeetan 0.3mg/ml / 5mg/ml eye drops preservative free	Bimatoprost and timolol
Ganfort 0.3mg/ml / 5mg/ml eye drops 0.4ml unit dose	Bimatoprost and timolol
Ganfort 0.3mg/ml / 5mg/ml eye drops	Bimatoprost and timolol
Travoprost 40micrograms/ml / Timolol 5mg/ml eye drops	Travoprost and Timolol
DuoTrav 40micrograms/ml / 5mg/ml eye drops	Travoprost and Timolol

Treatment - naming per DM+D (AMP)	Product link to available FDC category
Simbrinza 10mg/ml / 2mg/ml eye drops	Brinzolamide and brimonidine
Combigan eye drops (priced by 3*5ml pack)	Brimonidine and timolol
Combigan eye drops (priced by 1*5ml pack)	Brimonidine and timolol

Abbreviations: AMP – Actual medicinal product; DM+D – Dictionary of medicines and devices; FDC – Fixed-dose combination

As suggested by the EAG, adverse event rates and associated resource use have been separated into mild, moderate, and severe in the model. The EAG's recommended resource use has been applied (applying clinician-suggested values for severe occurrence, EAG-suggested values for moderate occurrence, and assuming no cost is incurred for mild occurrence). In line with EAG recommendation, some costs have also been removed or applied only for a smaller proportion of patients.

Sources for AE rates, resource use, and cost per item remain unchanged from the Technical Engagement stage. The AE associated cost and resource use are reported in the Technical Engagement response form.

Miscellaneous unit costs and resource use

The original submission included selective laser trabeculoplasty (SLT) and trabeculectomy as add-on surgical treatments (miscellaneous costs). Considering the updates to the model structure, with a shorter time horizon, earlier stage of treatment pathway, and cost-focus, these add-on costs have been removed from the model. This reflects the equivalence of these add-on costs across netarsudil-latanoprost and all comparators, with update dictated strictly by discontinuation rate, which is equivalent across all comparators in this model. Miscellaneous costs and resource use are the same as that presented in the model as part of the Technical Engagement response. The model is intended to show the costs of a patient's treatment within one year, and not to represent a patient's entire time on treatment, so SLT and trabeculectomy costs have not been included to reflect this.

Clinical expert validation

The clinical expert validation available remains as that presented in Section B.3.5.2 to Section B.3.5.4 and Section B.3.12 of Document B of the original submission. This included internal and external validation of the model. This was developed internally by health economists and checked for accuracy by other analysts not involved in the development. External validation of the model was performed in multiple stages with multiple clinical experts.

Key stages of validation relevant to this analysis included:

- Consultation with a UK expert in the pre-development stage to ratify the appropriateness and suitability of the model structure, health states and choice of outcomes.

- A stage of validation interviews with three clinical experts to identify data sources and confirmation of model inputs, including typical resource use for treatment of AEs and outcomes for clinical meaningfulness.

- Clinical validation and confirmation of the variables which constituted treatment effect modifiers and prognostic variables for inclusion in the matching adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) comparisons, prior to conducting the indirect treatment comparison (ITC) analyses.

- A revalidation of inputs in the context of the results they generated, to assess reflection of clinical practice. This included estimates of safety of netarsudil-latanoprost, and comparators derived from the ITC as well as key modelling assumptions.

- A validation of typical management and resource use for treatment of AEs.

Uncertainties in the inputs and assumptions

Most uncertainty in the model cost and resource use estimates has been resolved in discussion with the EAG and NICE committee, including the use of a combination of

the Company's and the EAG's preferred AE assumptions around AE rates and duration.

To reflect the resolution of most uncertainty in the model, a probabilistic sensitivity analyses has not been included in the current model. A one-way sensitivity analysis has, however, been included for the number of drops per pack and AE rates to address the remaining uncertainty in the model.

The conversion of ml to drops per pack is varied from the base case of 0.035 (71.43 drops per pack) to a lower bound of 0.028 (89.29 drops per pack) and higher bound of 0.042 (59.52 drops per pack) based on the assumed standard error (SE).

An AE rate multiplier has been added to vary AE rates across all comparators between 50% and 150% of the base-case rate.

A scenario analysis was also included where an alternative wastage assumption was explored, and this is further detailed in Section B.4 Cost-comparison analysis in the scenario analysis that wastage would be bound by model cycles, therefore no product would be transferred to the next cycle, and a new pack of product would be started every month. This is in contrast to the base-case analysis, where a patient only receives a new product when the current product expires, thus there may be more than one drug cost accrued per cycle and is more reflective of real-world practice.

B.4.3 Base-case results

This section presents the base-case results of the cost-minimisation analysis comparing netarsudil-latanoprost with 23 branded and generic FDC products as comparators in a population of patients with POAG or OHT. Base-case results are presented using the list price due to be set for netarsudil-latanoprost, as presented in Section B.4 Cost-comparison analysis.

The cost-minimisation analysis was conducted against all comparators, regardless of whether the FDC treatment was a branded or generic product. However, netarsudil-latanoprost is anticipated to be primarily positioned in the same line of treatment as

other branded products after a patient has experienced insufficient reduction in IOP following treatment with a generic PGA.

As discussed in Section B.1 Decision problem, description of the technology and clinical care pathway, as the only PGA-containing FDC product that does not contain a beta blocker, netarsudil-latanoprost is particularly suitable as an alternative treatment option for patients who are not suitable for beta blocker-containing ocular agents or for patients who are intolerant to beta blocker-containing ocular agents because of intolerance.

Table 14 shows the deterministic base-case results at a time horizon of one year, and the incremental costs of netarsudil-latanoprost against each comparator.

In the base-case analysis, netarsudil-latanoprost was associated with lower total cost per patient (£[redacted]) when compared with generic bimatoprost-timolol, Eyzeetan (bimatoprost-timolol), Ganfort drops (bimatoprost-timolol), Medox (latanoprost-timolol), Duotrav (travoprost-timolol), Xalacom (latanoprost-timolol), Fixapost (latanoprost-timolol), Cosopt multi dose 10ml (dorzolamide-timolol), Taptiqom (tafluprost-timolol), generic 60.2ml dorzolamide-timolol, Ganfort single dose units (bimatoprost-timolol), and Cosopt single dose 0.2ml unit dose (dorzolamide-timolol). However, a large proportion of this cost per patient constitutes disease management costs (£415.14), which is the same across all treatments. This indicates that netarsudil-latanoprost is cost-saving versus these comparators over a one-year time horizon. These 13 comparators take up [redacted]% of the overall (all branded and generic products) market share, demonstrating that netarsudil-latanoprost is more cost-saving than a large proportion of the current market.

When compared with branded products only, netarsudil-latanoprost was associated with lower total costs per patient than 11 of the 18 branded products. The incremental cost per patient of netarsudil-latanoprost versus other comparators ranged from -£[redacted] (Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops) to £[redacted] (Cosopt 20mg/ml / 5mg/ml eye drops 0.2ml unit dose preservative free).

Table 14: Base-case results

Rank	Technology (AMP naming)	Acquisition costs per patient per year (£)	Adverse event costs per patient per year (£)	Disease management costs per patient per year (£)	Cost per patient per year (£)	Incremental cost per patient per year (£)
1	Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops	£20.47	£4.95	£415.14	£440.56	[redacted]
2	Brinzolamide 10mg/ml / Timolol 5mg/ml eye drops	£38.17	£1.19	£415.14	£454.50	[redacted]
3	Travoprost 40micrograms/ml / Timolol 5mg/ml eye drops	£54.30	£7.45	£415.14	£476.89	[redacted]
4	Latanoprost 50micrograms/ml / Timolol 5mg/ml eye drops	£62.61	£4.74	£415.14	£482.49	[redacted]
5	Eylamdo 20mg/ml / 5mg/ml eye drops	£97.89	£4.95	£415.14	£517.98	[redacted]
6	Vizidor Duo 20mg/ml / 5mg/ml eye drops	£98.01	£4.95	£415.14	£518.10	[redacted]
7	Simbrinza 10mg/ml / 2mg/ml eye drops	£111.13	£8.22	£415.14	£534.50	[redacted]
8	Combigan eye drops (priced by 3*5ml pack)	£116.23	£3.44	£415.14	£534.81	[redacted]
9	Combigan eye drops (priced by 1*5ml pack)	£120.40	£3.44	£415.14	£538.98	[redacted]
10	Cosopt 20mg/ml / 5mg/ml eye drops	£121.00	£4.95	£415.14	£541.10	[redacted]
11	Azarga 10mg/ml / 5mg/ml eye drops	£133.04	£1.19	£415.14	£549.38	[redacted]

Rank	Technology (AMP naming)	Acquisition costs per patient per year (£)	Adverse event costs per patient per year (£)	Disease management costs per patient per year (£)	Cost per patient per year (£)	Incremental cost per patient per year (£)
12	Roclanda 50micrograms/ml + 200micrograms/ml eye drops	£120.40	[redacted]	£415.14	[redacted]	N/A
13	Bimatoprost 300micrograms/ml / Timolol 5mg/ml eye drops	£144.51	£4.07	£415.14	£563.73	[redacted]
14	Eyzeetan 0.3mg/ml / 5mg/ml eye drops preservative free	£144.51	£4.07	£415.14	£563.73	[redacted]
15	Medox 50micrograms/ml / 5mg/ml eye drops	£168.56	£4.74	£415.14	£588.44	[redacted]
16	DuoTrav 40micrograms/ml / 5mg/ml eye drops	£167.96	£7.45	£415.14	£590.55	[redacted]
17	Xalacom eye drops	£172.41	£4.74	£415.14	£592.30	[redacted]
18	Fixapost 50micrograms/ml / 5mg/ml eye drops 0.2ml unit dose	£174.21	£4.74	£415.14	£594.09	[redacted]
19	Cosopt iMulti 20mg/ml / 5mg/ml eye drops preservative free	£180.80	£4.95	£415.14	£600.89	[redacted]
20	Ganfort 0.3mg/ml / 5mg/ml eye drops	£182.86	£4.07	£415.14	£602.08	[redacted]
21	Ganfort 0.3mg/ml / 5mg/ml eye drops 0.4ml unit dose	£183.09	£4.07	£415.14	£602.31	[redacted]
22	Taptiqom 15micrograms/ml / 5mg/ml eye drops 0.3ml unit dose	£187.25	£3.72	£415.14	£606.12	[redacted]

Rank	Technology (AMP naming)	Acquisition costs per patient per year (£)	Adverse event costs per patient per year (£)	Disease management costs per patient per year (£)	Cost per patient per year (£)	Incremental cost per patient per year (£)
23	Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops 0.2ml unit dose preservative free	£230.64	£4.95	£415.14	£650.74	[redacted]
24	Cosopt 20mg/ml / 5mg/ml eye drops 0.2ml unit dose preservative free	£369.21	£4.95	£415.14	£789.31	[redacted]

Abbreviations: AMP – Actual medicinal product

B.4.4 Sensitivity and scenario analyses

As noted in Section B.4 Cost-comparison analysis few unaddressed uncertainties in inputs were present in the cost-minimisation model, following discussions with the EAG and NICE. While a probabilistic sensitivity analysis was not deemed necessary, a one-way sensitivity analysis was conducted for the number of drops per pack and AE rates.

The one-way sensitivity analysis (OWSA) was performed using a SE approach. Where the SE was not available for a parameter, the SE was assumed to be 20% of the mean value. Based on the mean and the SE of each parameter, the parameter was then varied using a 95% confidence interval based on the distribution of the parameter (Gamma in these instances). The OWSA was performed for netarsudil-latanoprost compared with each FDC comparator in the model, with results presented in to Table 37.

For comparators formulated as a single-dose pack (unit dose), varying the pack to drop conversion rate did not result in any changes to the resulting costs as expected. Varying the AE multiplier model parameter had a minimal impact on the results, with a difference in costs ranging from £4 to £6, showing that the model was not sensitive to the AE multiplier.

Table 15 Tabulated OWSA results for Azarga (brinzolamide-timolol)

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	-£4	-£1	£4
AE multiplier	£1	-£5	£6

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 16 Tabulated OWSA results for generic brinzolamide-timolol

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	-£82	-£105	£23
AE multiplier	-£94	-£100	£6

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 17 Tabulated OWSA results for generic dorzolamide-timolol, 60.2ml

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	£121	£88	£34
AE multiplier	£102	£97	£4

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 18 Tabulated OWSA results for generic dorzolamide-timolol, 5ml

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	-£93	-£120	£28
AE multiplier	-£109	-£113	£4

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 19 Tabulated OWSA results for Cosopt (dorzolamide-timolol), 5ml

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	-£10	-£10	£0
AE multiplier	-£8	-£12	£4

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 20 Tabulated OWSA results for Cosopt (dorzolamide-timolol) single dose, 60.2ml

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	£260	£226	£34
AE multiplier	£240	£236	£4

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 21 Tabulated OWSA results for Cosopt (dorzolamide-timolol) multi dose, 10ml

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	£72	£38	£34
AE multiplier	£52	£47	£4

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 22 Tabulated OWSA results for Eylamdo (dorzolamide-timolol)

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	-£29	-£36	£6
AE multiplier	-£31	-£36	£4

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 23 Tabulated OWSA results for Vizidor (dorzolamide-timolol)

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	-£29	-£35	£6
AE multiplier	-£31	-£35	£4

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 24 Tabulated OWSA results for generic latanoprost-timolol

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	-£58	-£74	£16
AE multiplier	-£67	-£71	£4

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 25 Tabulated OWSA results for Fixapost (latanoprost-timolol)

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	£65	£31	£34
AE multiplier	£45	£41	£4

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 26 Tabulated OWSA results for Medox (latanoprost-timolol)

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	£28	£42	£13
AE multiplier	£39	£35	£4

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 27 Tabulated OWSA results for Xalacom (latanoprost-timolol)

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	£31	£46	£15
AE multiplier	£43	£39	£4

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 28 Tabulated OWSA results for Taptiqom (tafluprost-timolol)

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	£77	£43	£34
AE multiplier	£57	£52	£5

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 29 Tabulated OWSA results for generic bimatoprost-timolol

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	£8	£27	£18
AE multiplier	£15	£10	£5

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 30 Tabulated OWSA results for Eyzeetan (bimatoprost-timolol)

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	£8	£27	£18
AE multiplier	£15	£10	£5

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 31 Tabulated OWSA results for Ganfort drops (bimatoprost-timolol)

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	£73	£39	£34
AE multiplier	£53	£48	£5

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 32 Tabulated OWSA results for Ganfort single dose units (bimatoprost-timolol)

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	£40	£72	£32
AE multiplier	£53	£49	£5

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 33 Tabulated OWSA results for generic travoprost-timolol

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	£62	£81	£18
AE multiplier	£73	£76	£3

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 34 Tabulated OWSA results for Duotrav (travoprost-timolol)

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	£31	£44	£13
AE multiplier	£41	£38	£3

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 35 Tabulated OWSA results for Simbrinza (brinzolamide-brimonidine)

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	-£15	-£18	£3

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
AE multiplier	-£15	-£18	£3

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 36 Tabulated OWSA results for Combigan (brimonidine-timolol), 3*5ml

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	£5	-£28	£34
AE multiplier	-£14	-£19	£5

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Table 37 Tabulated OWSA results for Combigan (brimonidine-timolol), 1*5ml

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
Pack to drop conversion rate, ml in drop	£12	£12	£0
AE multiplier	£10	£15	£5

Abbreviations: AE – Adverse event; OWSA – One-way sensitivity analysis

Scenario analyses: Wastage bound by model cycles

A scenario analysis was conducted, varying the wastage calculations for each comparator. While the base case uses the 'real-world' setting, the scenario uses the 'Bound by model cycles' setting (Table 38), as detailed earlier in B.4 Cost-comparison analysis.

In the scenario, adverse event costs per year and disease management costs per year were unchanged, with total costs impacted through acquisitions costs per year only.

Alike the base case, netarsudil-latanoprost ranks 12th out of the comparators in terms of lowest cost per patient, per year. This equivalent rank demonstrates a lack of sensitivity to the change in wastage assumption.

Acquisition costs varied broadly across the comparators as a result of the methodology:

- For five comparators (Generic dorzolamide-timolol 60.2ml; Cosopt, single dose dorzolamide-timolol 60.2ml; Cosopt multi dose dorzolamide-timolol 10ml; Fixapost - latanoprost-timolol; Taptiqom - tafluprost-timolol; Ganfort drops - bimatoprost-timolol) there was no change, due to the unit dosing and consequent avoidance of wastage.

- For the remaining 19 comparators, increases in acquisition costs per patient were observed, ranging from £1.49 (Cosopt dorzolamide-timolol 5ml) to £48.58 (Ganfort single dose units – bimatoprost-timolol). While considerable price changes were observed for Ganfort single dose units, Eyzeetan (£38.35), and generic bimatoprost-timolol (£38.35), most comparators had price changes of less than £13.00. The susceptibility of these three comparators to the methodology change in wastage is a result of the low percentage usage of a pack per cycle (71%) relative to the other comparators. However, as stated in Section B.4.2, wastage of the remaining pack is not expected to occur at this rate in the real-world setting.

In conclusion, the change in wastage methodology is not crucial in determining the cost-minimisation results. While three products experience a notable increase in costs, the scenario is considered unlikely in real-world practice.

Table 38: Scenario analysis results (Wastage bound by model cycles)

Rank	Technology (AMP naming)	Acquisition costs per patient per year (£)	Adverse event costs per patient per year (£)	Disease management costs per patient per year (£)	Cost per patient per year (£)	Incremental cost per patient per year (£)
1	Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops	£21.95	£4.95	£415.14	£442.05	[redacted]
2	Brinzolamide 10mg/ml / Timolol 5mg/ml eye drops	£40.94	£1.19	£415.14	£457.27	[redacted]
3	Travoprost 40micrograms/ml / Timolol 5mg/ml eye drops	£58.24	£7.45	£415.14	£480.83	[redacted]
4	Latanoprost 50micrograms/ml / Timolol 5mg/ml eye drops	£67.15	£4.74	£415.14	£487.03	[redacted]
5	Eylamdo 20mg/ml / 5mg/ml eye drops	£104.99	£4.95	£415.14	£525.09	[redacted]
6	Vizidor Duo 20mg/ml / 5mg/ml eye drops	£105.12	£4.95	£415.14	£525.22	[redacted]
7	Combigan eye drops (priced by 3*5ml pack)	£116.23	£3.44	£415.14	£534.81	[redacted]
8	Simbrinza 10mg/ml / 2mg/ml eye drops	£119.20	£8.22	£415.14	£542.56	[redacted]
9	Combigan eye drops (priced by 1*5ml pack)	£129.14	£3.44	£415.14	£547.72	[redacted]
10	Cosopt 20mg/ml / 5mg/ml eye drops	£129.79	£4.95	£415.14	£549.88	[redacted]
11	Azarga 10mg/ml / 5mg/ml eye drops	£142.70	£1.19	£415.14	£559.03	[redacted]
12	Roclanda 50micrograms/ml + 200micrograms/ml eye drops	£129.14	[redacted]	£415.14	[redacted]	N/A

Rank	Technology (AMP naming)	Acquisition costs per patient per year (£)	Adverse event costs per patient per year (£)	Disease management costs per patient per year (£)	Cost per patient per year (£)	Incremental cost per patient per year (£)
13	Fixapost 50micrograms/ml / 5mg/ml eye drops 0.2ml unit dose	£174.21	£4.74	£415.14	£594.09	[redacted]
14	Medox 50micrograms/ml / 5mg/ml eye drops	£180.80	£4.74	£415.14	£600.68	[redacted]
15	Cosopt iMulti 20mg/ml / 5mg/ml eye drops preservative free	£180.80	£4.95	£415.14	£600.89	[redacted]
16	Bimatoprost 300micrograms/ml / Timolol 5mg/ml eye drops	£182.86	£4.07	£415.14	£602.08	[redacted]
17	Eyzeetan 0.3mg/ml / 5mg/ml eye drops preservative free	£182.86	£4.07	£415.14	£602.08	[redacted]
18	Ganfort 0.3mg/ml / 5mg/ml eye drops	£182.86	£4.07	£415.14	£602.08	[redacted]
19	DuoTrav 40micrograms/ml / 5mg/ml eye drops	£180.15	£7.45	£415.14	£602.74	[redacted]
20	Xalacom eye drops	£184.93	£4.74	£415.14	£604.81	[redacted]
21	Taptiqom 15micrograms/ml / 5mg/ml eye drops 0.3ml unit dose	£187.25	£3.72	£415.14	£606.12	[redacted]
22	Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops 0.2ml unit dose preservative free	£230.64	£4.95	£415.14	£650.74	[redacted]
23	Ganfort 0.3mg/ml / 5mg/ml eye drops 0.4ml unit dose	£231.68	£4.07	£415.14	£650.89	[redacted]
24	Cosopt 20mg/ml / 5mg/ml eye drops 0.2ml unit dose preservative free	£369.21	£4.95	£415.14	£789.31	[redacted]

Scenario analyses: AE costs excluded

A scenario analysis was conducted where the costs of AEs for all products were excluded. As a number of the AEs included in the costs of the base-case analysis would be considered for routine management, and are included on the understanding of conservative presentation of results, the scenario analysis could be more deemed reflective of real-world clinical practice. Table 39 displays the results for the exclusion of AEs scenario for the 1-year time horizon.

Netarsudil-latanoprost ranks 9th in terms of cost per patient, compared to 12th rank in the base case. This reflects that in the base case, costs incurred from AEs are comparatively higher for netarsudil-latanoprost than some other comparators. Given the nature, low severity, and low-cost treatment of the AEs incurred by treatment with netarsudil-latanoprost, the base case likely overestimates costs and worsens the relative rank of netarsudil-latanoprost.

The 15 comparators that netarsudil-latanoprost is cheaper than take up [redacted]% of the overall (all branded and generic products) market share, demonstrating that in this scenario netarsudil-latanoprost is cost-saving against a large proportion of the current market, including all the bimatoprost-timolol combinations, as used in the MERCURY 3 trial.

Table 39: Scenario analysis results (AE costs excluded)

Rank	Technology (AMP naming)	Acquisition costs per patient per year (£)	Adverse event costs per patient per year (£)	Disease management costs per patient per year (£)	Cost per patient per year (£)	Incremental cost per patient, per year (£)
1	Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops	£20.47	£0.00	£415.14	£435.61	-£99.93
2	Brinzolamide 10mg/ml / Timolol 5mg/ml eye drops	£38.17	£0.00	£415.14	£453.31	-£82.23
3	Travoprost 40micrograms/ml / Timolol 5mg/ml eye drops	£54.30	£0.00	£415.14	£469.44	-£66.10
4	Latanoprost 50micrograms/ml / Timolol 5mg/ml eye drops	£62.61	£0.00	£415.14	£477.75	-£57.79
5	Eylamdo 20mg/ml / 5mg/ml eye drops	£97.89	£0.00	£415.14	£513.03	-£22.52
6	Vizidor Duo 20mg/ml / 5mg/ml eye drops	£98.01	£0.00	£415.14	£513.15	-£22.39
7	Simbrinza 10mg/ml / 2mg/ml eye drops	£111.13	£0.00	£415.14	£526.27	-£9.27
8	Combigan eye drops (priced by 3*5ml pack)	£116.23	£0.00	£415.14	£531.37	-£4.18
9	Roclanda 50micrograms/ml + 200micrograms/ml eye drops	£120.40	£0.00	£415.14	£535.54	N/A
10	Combigan eye drops (priced by 1*5ml pack)	£120.40	£0.00	£415.14	£535.54	£0.00
11	Cosopt 20mg/ml / 5mg/ml eye drops	£121.00	£0.00	£415.14	£536.14	£0.60
12	Azarga 10mg/ml / 5mg/ml eye drops	£133.04	£0.00	£415.14	£548.19	£12.64

Rank	Technology (AMP naming)	Acquisition costs per patient per year (£)	Adverse event costs per patient per year (£)	Disease management costs per patient per year (£)	Cost per patient per year (£)	Incremental cost per patient, per year (£)
13	Bimatoprost 300micrograms/ml / Timolol 5mg/ml eye drops	£144.51	£0.00	£415.14	£559.66	£24.11
14	Eyzeetan 0.3mg/ml / 5mg/ml eye drops preservative free	£144.51	£0.00	£415.14	£559.66	£24.11
15	DuoTrav 40micrograms/ml / 5mg/ml eye drops	£167.96	£0.00	£415.14	£583.10	£47.56
16	Medox 50micrograms/ml / 5mg/ml eye drops	£168.56	£0.00	£415.14	£583.70	£48.16
17	Xalacom eye drops	£172.41	£0.00	£415.14	£587.56	£52.01
18	Fixapost 50micrograms/ml / 5mg/ml eye drops 0.2ml unit dose	£174.21	£0.00	£415.14	£589.35	£53.81
19	Cosopt iMulti 20mg/ml / 5mg/ml eye drops preservative free	£180.80	£0.00	£415.14	£595.94	£60.39
20	Ganfort 0.3mg/ml / 5mg/ml eye drops	£182.86	£0.00	£415.14	£598.00	£62.46
21	Ganfort 0.3mg/ml / 5mg/ml eye drops 0.4ml unit dose	£183.09	£0.00	£415.14	£598.23	£62.69
22	Taptiqom 15micrograms/ml / 5mg/ml eye drops 0.3ml unit dose	£187.25	£0.00	£415.14	£602.39	£66.85
23	Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops 0.2ml unit dose preservative free	£230.64	£0.00	£415.14	£645.79	£110.24

Rank	Technology (AMP naming)	Acquisition costs per patient per year (£)	Adverse event costs per patient per year (£)	Disease management costs per patient per year (£)	Cost per patient per year (£)	Incremental cost per patient, per year (£)
24	Cosopt 20mg/ml / 5mg/ml eye drops 0.2ml unit dose preservative free	£369.21	£0.00	£415.14	£784.35	£248.81

Subgroup analysis

No analysis of subgroups had been undertaken as there were no subgroups of interest.

B.4.6 Interpretation and conclusions of economic evidence

The results from the deterministic base-case analysis show that, over a one-year time horizon, netarsudil-latanoprost is associated with lower costs per patient (£[redacted]) when compared with 13 of the 23 comparators, which make up approximately [redacted]% of the overall market share, demonstrating that netarsudil-latanoprost is cost-saving versus a large proportion of these comparators. Results from the OWSA and scenario analyses were also robust and demonstrated similar findings.

Netarsudil-latanoprost, as a new class of medication with a novel mechanism of action that targets the trabecular meshwork and is the only PGA-containing FDC product that does not contain a beta blocker. All of the comparators presented in this analysis except Simbrinza (brinzolamide-brimonidine) contain beta blockers as an active ingredient. This positions netarsudil-latanoprost as a unique and novel treatment option for patients lacking alternative treatment options where a beta blocker is not appropriate, or where patients show insufficient response to a generic FDC. Netarsudil-latanoprost can therefore provide a treatment option in patients with a previously unmet need. This will also further reduce the need for glaucoma surgery and decrease the risk of developing irreversible sight loss in POAG or OHT patients, while decreasing the substantial direct and indirect costs associated with the disease. Furthermore, patients with POAG or OHT experience a reduction in QoL and significant challenges in daily life as their visual function deteriorates and conditions increase in severity, highlighting the importance of a treatment that can alleviate disease burden.

POAG and OHT are associated with considerable costs to the healthcare system, with an expected rise in the annual cost incurred by the NHS over the coming years due to factors including an ageing population. Modelling projections estimate that the number of glaucoma patients in the UK is expected to rise by 44% between 2015 and 2035, thus having a significant economic impact on the NHS.[31] There is therefore an

increasingly urgent need for a cost-saving and effective treatment for patients with POAG or OHT to reduce the economic burden on the healthcare system.

Overall, this economic analysis shows that netarsudil-latanoprost may be considered a cost-saving treatment for patients with POAG or OHT. It will provide an alternative treatment option in the management of these conditions, with a novel mechanism of action, for patients who are underserved by currently available therapies.

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B.6 Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

C1.1 SmPC

C1.2 UK public assessment report

Please see Appendix C from the original submission for details of the SmPC and European public assessment report.

Appendix D: Identification, selection and synthesis of clinical evidence

D1.1 Identification and selection of relevant studies

The process and methods of the SLR conducted can be found in the response to Issue 1 and Appendix of the Technical Engagement response form.

D1.2 Participant flow in the relevant randomised control trials

Please see Appendix D of Document B from the original submission for details of the RCT participant flow.

D1.3 Quality assessment for each study

Please see Appendix D of Document B from the original submission, as well as the Appendix of the Technical Engagement response form for the quality assessment details for the studies.

Appendix E: Subgroup analysis

Please see Appendix E of Document B from the original submission for details of previous subgroup analyses.

Appendix F: Adverse reactions

Please see Section B.2.10 of Document B from the original submission for details regarding adverse reactions.

Appendix G: Cost and healthcare resource identification, measurement and valuation

Please see Appendix I from the original submission for details on the cost and resource use studies identified.

Appendix H: Price details of treatments included in the submission

H1.1 Price of intervention

Name	Form	Dose per unit	Pack size	List price	Source	PAS price
Roclanda (netarsudil-latanoprost)	Suspension	0.05mg/ml	2.50ml (50.00 drops)	10.00	Santen	N/A
Abbreviations: PAS - Patient access scheme						

H1.2 Price of comparators and subsequent treatments

Table Details of comparators and subsequent treatment costs, including concomitant medicines, for each formulation used in the model

Name	Form	Dose per unit	Pack size	List price	Source
Azarga (brinzolamide-timolol)	Suspension	10mg/ml + 5mg/ml	5 ml	11.05	BNF[3]
Generic (brinzolamide-timolol)	Suspension	10 mg/ml + 5mg/ml	5 ml	4.04	BNF[3]
Generic, 60.2ml (dorzolamide-timolol)	Suspension	20 mg/ml + 5mg/ml	60.2 ml	28.59	BNF[4]
Generic, 5ml (dorzolamide-timolol)	Suspension	20 mg/ml + 5mg/ml	5 ml	2.10	BNF[4]
Cosopt, single dose 5ml (dorzolamide-timolol)	Suspension	20 mg/ml + 5mg/ml	5 ml	10.05	BNF[4]
Cosopt, single dose 60.2ml (dorzolamide-timolol)	Suspension	20 mg/ml + 5mg/ml	60.2 ml	28.59	BNF[4]
Cosopt, multi dose 10ml (dorzolamide-timolol)	Suspension	20 mg/ml + 5mg/ml	10 ml	28.00	BNF[4]
Eylamdo (dorzolamide-timolol)	Suspension	20 mg/ml + 5mg/ml	5 ml	8.13	BNF[4]
Vizidor (dorzolamide-timolol)	Suspension	20 mg/ml + 5mg/ml	5 ml	8.14	BNF[4]
Generic (latanoprost-timolol)	Suspension	50 mg/ml + 5 mg/ml	2.5 ml	3.33	BNF[10]
Fixapost (latanoprost-timolol)	Suspension	50 mg/ml + 5 mg/ml	30.2 ml	13.49	BNF[10]
Medox (latanoprost-timolol)	Suspension	50 mg/ml + 5 mg/ml	2.5 ml	14.00	BNF[10]

Xalacom (latanoprost-timolol)	Suspension	50 mg/ml + 5 mg/ml	2.5 ml	14.32	BNF[10]
Taptiqom (tafluprost-timolol)	Suspension	15 mg/ml + 5mg/ml	30.3 ml	14.50	BNF[16]
Generic (bimatoprost-timolol)	Suspension	300 mg/ml + 5mg/ml	3 ml	14.16	BNF[17]
Eyzeetan (bimatoprost-timolol)	Suspension	300 mg/ml + 5mg/ml	3 ml	14.16	BNF[17]
Ganfort drops (bimatoprost-timolol)	Suspension	300 mg/ml + 5mg/ml	3 ml	14.16	BNF[17]
Ganfort single dose units (bimatoprost-timolol)	Suspension	300 mg/ml + 5mg/ml	30.4 ml	17.94	BNF[17]
Generic (travoprost-timolol)	Suspension	40 mg/ml + 5mg/ml	2.5 ml	7.88	BNF[23]
Duotrav (travoprost-timolol)	Suspension	40 mg/ml + 5mg/ml	2.5 ml	13.95	BNF[23]
Simbrinza (brinzolamide-brimonidine)	Suspension	10 mg/ml + 2mg/ml	5 ml	9.23	BNF[24]
Combigan, 3*5ml (brimonidine-timolol)	Suspension	2 mg/ml + 5mg/ml	35 ml	27.00	BNF[25]
Combigan, 5ml (brimonidine-timolol)	Suspension	2 mg/ml + 5mg/ml	5 ml	10.00	BNF[25]
Abbreviations: PAS - Patient access scheme					

Appendix I: Checklist of confidential information

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Netarsudil-latanoprost for previously treated open-angle glaucoma or ocular hypertension [ID1363]

Summary of Information for Patients (SIP)

July 2023

File name	Version	Contains confidential information	Date
ID1363_Netarsudil-latanoprost Summary of Information for Patients_v2.0_05JUL23	v2.0	No	05/07/23

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Netarsudil-latanoprost eye drops is sold under the brand name Roclanda®.

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Netarsudil-latanoprost is being appraised by NICE for adult patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT) for whom monotherapy (one single treatment) with a prostaglandin or netarsudil provides insufficient reduction in intraocular pressure (IOP) (fluid pressure of the eye).[1]

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The Medicines and Healthcare Regulatory Agency (MHRA) and European Medicines Agency (EMA) granted a marketing authorisation for netarsudil-latanoprost on the 12th April 2021 and 12th November 2020, respectively: https://products.mhra.gov.uk/search/?search=roclanda&page=1 https://www.ema.europa.eu/en/medicines/human/EPAR/roclanda

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Santen has supported Glaucoma UK on matters such as patient adherence through "Know your drops" campaign and disease awareness leaflets. Santen has also supported Fight for Sight through a donation towards their publication "Time to Focus".

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Glaucoma is the name for a group of eye conditions that cause sight loss because of damage to the optic nerve, which connects the eye to the brain.[2] Symptoms include loss of the field of vision, and reduced vision.[3] Severely raised IOP (fluid pressure of the eye) causes a marked loss of sight, halos around bright lights, and severe eye pain that comes on suddenly. This can be accompanied by redness and tenderness of the eye, headaches, nausea (sickness) and vomiting.

Glaucoma damage can be prevented if detected and treated early. However, in most patients it tends to develop slowly and does not cause noticeable symptoms until severe damage has already occurred. Sight loss from damage to the optic nerve is currently irreversible And it's the second leading cause of blindness in the world.[4]

An IOP measure of between 11 and 21 mmHg is considered normal.[5] Elevated IOP (i.e., IOP >21 mmHg) is considered the most significant risk factor for developing glaucoma.[6] Therefore controlling IOP is critical to prevent progression to glaucoma and damage to the eye.

POAG is defined by the European Glaucoma Society (EGS) as a chronic (lifelong), progressive, potentially blinding, and irreversible eye disease causing optic nerve damage resulting in loss of field vision and reduced vision. Visual disability is usually prevented by early diagnosis and treatment.[7]

In the United Kingdom (UK) POAG is the most common form of glaucoma. It is estimated that about 2% of people aged 40 years or over have POAG, and this rises to almost 10% in people older than 75 years.[8] Around half of all people in the UK with POAG have not been diagnosed, as people with the condition are typically unaware that they have it.[9,10]

OHT is the term used to describe elevated IOP, that is, IOP greater than 21 mmHg in the absence of optic nerve damage or visual field loss.[11] It can be present for many years without the development of glaucoma however, sustained elevation of IOP causes damage to the optic nerve head and is a major risk factor for the development of POAG.[5] Other risk factors for OHT developing into POAG includes corneal thickness and age.[6]

In the UK, OHT affects about 3-5% of people aged 40 years or over.[12] Treating patients with OHT is key in order to reduce the risk of progression into POAG, as demonstrated by the Ocular Hypertension Treatment Study (OHTS). Results from this study showed that the 5-year cumulative (total) probability of developing POAG in untreated OHT patients was 9.5% compared to 4.4% in treated OHT patients, demonstrating that if OHT is treated appropriately, then the risk of progression to POAG is reduced by approximately half.[13]

Patients with POAG or OHT who have elevated IOP despite existing treatment, are at continued high risk of vision loss.

Studies have determined that glaucoma has a significant negative impact on the psychological, social, and emotional functioning of patients and can leave affected individuals with anxiety, poor self-image, poor psychological well-being, and reduced confidence in healthcare.[14] Correlations have also been found between the quality of life of patients and visual field losses, vision-specific dependency and role difficulties.[15,16] Furthermore, the daily use of multiple medications and difficulty in using eye drops has also been negatively associated with patient quality of life.[17]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

For most people, the signs of glaucoma are first spotted opportunistically by an optometrist at a routine eye test in the community. The optometrist could carry out the following tests to diagnose glaucoma:

Visual field test
This tests whether your peripheral vision (i.e. the vision away from the centre, or everything you are not looking directly at) is healthy, or whether there are gaps.

Eye pressure test
A small puff of air is directed at your eye and bounces back onto the machine, which measures the pressure within the eye (intraocular pressure or IOP). If you have glaucoma or ocular hypertension, your eye pressure will normally be raised.

Optic nerve assessment
The optometrist looks at the back of the eye and may take a photograph. This is to check the health of the optic nerve. If you have glaucoma, the optic nerve will look different.

Depending on the risks the optometrist has identified and where you live, you may be referred directly to an ophthalmologist (an eye doctor) at a hospital. Alternatively, you may be referred to a specially-trained community optometrist.

When you see the glaucoma specialist, they will conduct more tests, including repeating some of those you have already had. The specialist will also look at other risk factors, such as ethnicity or family history of glaucoma. They will then decide whether you have glaucoma, or are at an increased risk, and whether you need to start treatment or not. Any vision lost to glaucoma is lost forever.

There are no additional tests or examinations required to use netarsudil-latanoprost compared to existing treatments.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The only modifiable risk factor for POAG or OHT is to reduce IOP, with the overall aim of treatment being to preserve sight. Achieving a reduction in IOP reduces pressure on the optic nerve and helps to stop further damage.

The three main mechanisms to control IOP are as follows: increasing aqueous humor (AH) outflow via (1) the trabecular meshwork (TM) pathway (conventional) and/or (2) via the uveoscleral outflow pathway (unconventional), or (3) decreasing the production of AH. In particular, the TM is responsible for approximately 70-96% of AH outflow.[18–20] There are currently no available fixed-dose combination (FDC) topical treatments that act on both the conventional and unconventional pathways, highlighting an urgent unmet need for a new treatment which does so.

Currently management of POAG and OHT requires chronic, life-long treatment with a spectrum of therapeutic options, including medications (such as prostaglandin analogues [PGAs] which act on the unconventional pathway, beta-blockers [BBs] and carbonic anhydrase inhibitors [CAIs], sympathomimetics, which act by reducing the production of AH), laser treatment (selective laser trabeculoplasty [SLT]) and surgery (trabecular stent bypass microsurgery).[21] The common goal amongst the various therapies is to lower IOP in order to prevent visual field loss in patients with OHT, and progression of field loss in patients with POAG. The impact of glaucoma on daily life is major.

Netarsudil and latanoprost can have a complementary effect on lowering IOP. Netarsudil improves trabecular outflow (conventional pathway), while latanoprost enhances uveoscleral outflow (unconventional pathway). By targeting both pathways, these medications can effectively reduce IOP in patients with glaucoma or ocular hypertension. [1] The fact that it is a FDC is also a benefit, as it is well known that FDCs not only improve adherence by reducing the medication burden, but also decrease the total amount of potentially delirious preservatives an eye is exposed to compared to free combination therapies.[22]

Netarsudil-latanoprost will fit into the existing treatment pathways for POAG and OHT at the point where patients need to step up from PGA and/or topical monotherapy onto a FDC therapy to control IOP, in line with its marketing authorisation.[1] Netarsudil-latanoprost will also be available for patients who have previously been treated with free combination therapies, in instances where IOP has not been sufficiently reduced, or when patients present with adherence problems. FDC therapies, when available, are preferable to multiple topical treatments, which may reduce adherence and increase exposure to preservatives, according to EGS guidelines.[23] The anticipated positioning of netarsudil-latanoprost in England is summarised below in Figure 1 for POAG, and Figure 2 for OHT, based on guidance from NICE.[12]

Figure 1: Anticipated positioning of netarsudil-latanoprost in patients with POAG

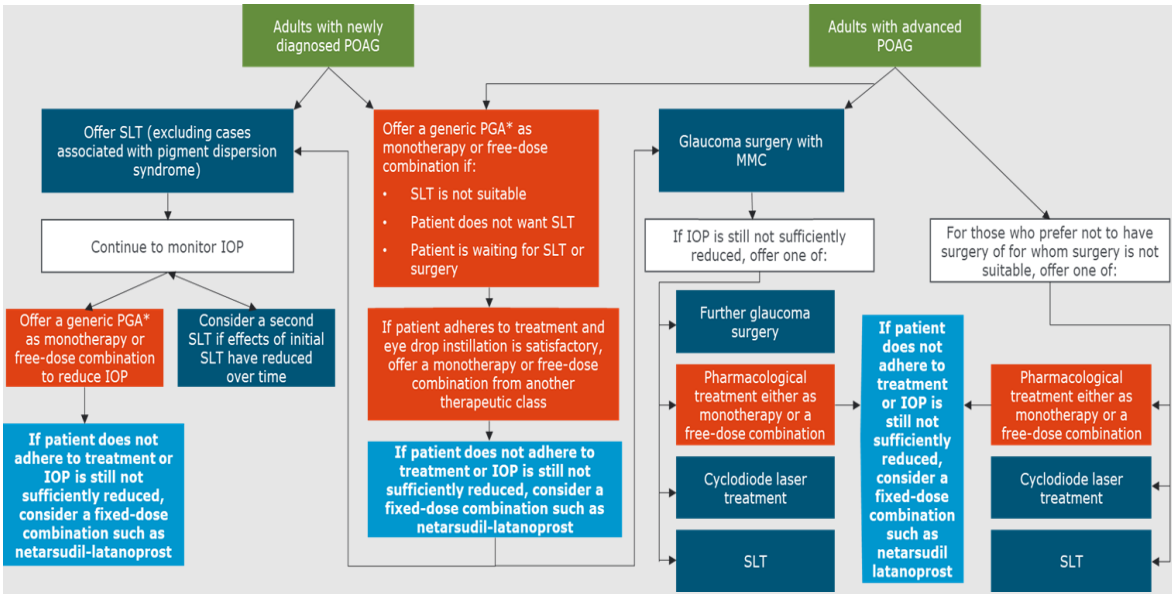
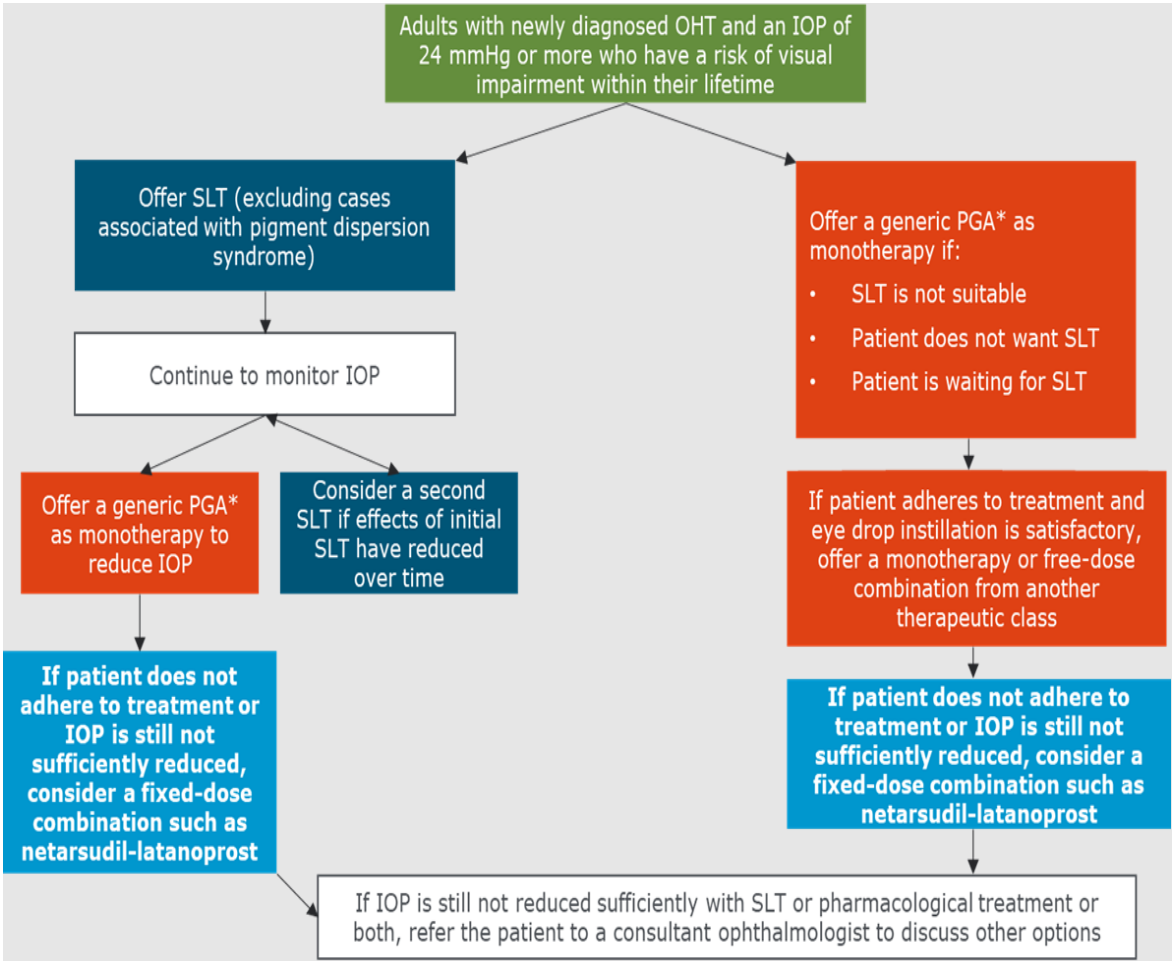


Figure 2: Anticipated positioning of netarsudil-latanoprost in patients with OHT



2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Patients with POAG or OHT face significant challenges on a daily basis due to their conditions. As vision starts to deteriorate, this has a detrimental effect on a patient's ability to walk, balance, read, drive, and limits their ability to carry out tasks such as grocery shopping and their employment. When walking becomes difficult, there is a higher risk of falls which restricts patients from engaging in physical activity, subsequently leading to a reduction in quality of life, an increase in morbidity and ultimately, could lead to an increased risk of mortality.[24]

These conditions also have a negative impact on the psychological, social, and emotional functioning of patients which can result in anxiety.[14] A diagnosis of POAG or OHT itself increases anxiety, and up to 80% of patients describe negative emotions upon receiving this, as they worry about possible blindness as a result.[25]

Studies have shown that the quality of life in POAG or OHT patients is often affected by the impairment of visual function, and as the severity of the conditions increases.[26] This highlights the importance of treatments that can lower IOP effectively to slow disease progression, which in turn should help to improve the quality of life of POAG or OHT patients.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Netarsudil-latanoprost contains two active substances: netarsudil, protein kinase (ROCK) inhibitor, and latanoprost, an isopropyl ester prodrug.[1] These two components lower IOP by increasing the outflow of aqueous humor (AH), via different mechanisms of action: the conventional (netarsudil) and unconventional (latanoprost) outflow. The combination of Netarsudil/ Latanoprost provides a better IOP reduction than latanoprost alone, which is one of the most frequently prescribed class of drugs for glaucoma

The three main mechanisms to control IOP are as follows: (1) increasing AH outflow via the TM pathway, (2) increasing AH outflow via the uveoscleral outflow pathway, or (3) decreasing the production of AH. In a healthy eye, the trabecular meshwork (TM) (conventional outflow) is responsible for approximately 70-96% of AH outflow.[18–20] In the

glaucomatous eye, the TM undergoes structural changes which leads to increased resistance in AH outflow (Figure 3).

Figure 3: Simplified view of the treatment of glaucoma using ROCK inhibitor drops

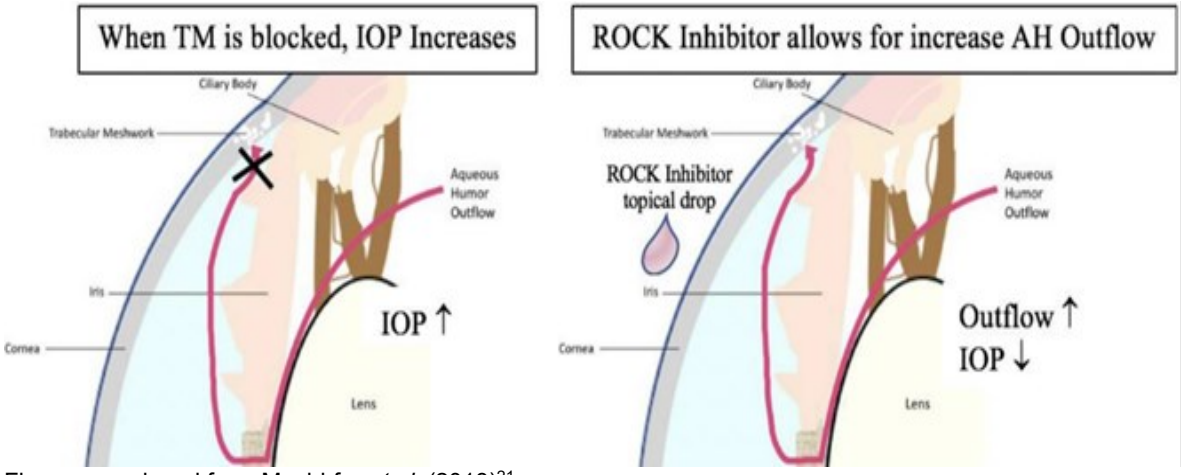


Figure reproduced from Moshirfar *et al.* (2018)[21]
Abbreviations: AH – aqueous humor; IOP – intraocular pressure; ROCK – Rho-(associated) coiled-coil containing protein kinase; TM – trabecular meshwork

Figure 4 below illustrates how netarsudil and latanoprost act on the TM.

Figure 4: Mechanism of action of netarsudil and latanoprost

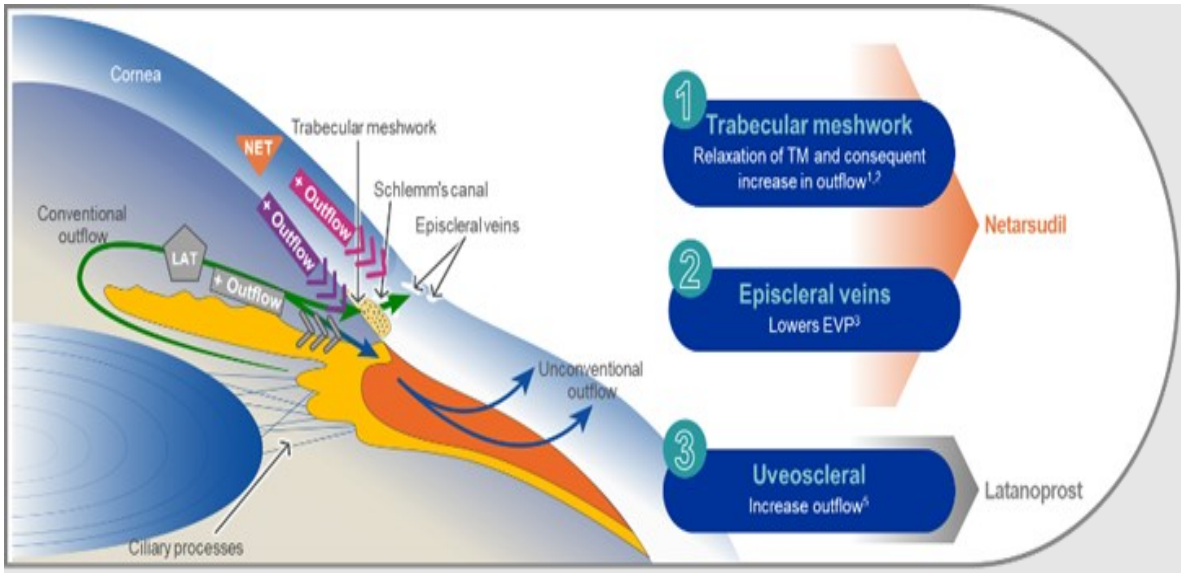


Figure reproduced from Rao *et al.* (2017), Rao *et al.* (2007), Sit *et al.* (2019), Wang *et al.* (2015), Toris *et al.* (2008)[27–31]
Abbreviations: EVP – episcleral venous pressure; LAT – latanoprost; NET – netarsudil; TM – trabecular meshwork.

Currently available pressure lowering medications, despite various combinations, mechanisms of actions, and analogues do not succeed in an adequate lowering of the intraocular pressure, particularly long term. There is a urgent unmet need for a combination that acts on both the conventional (netarsudil) and unconventional pathway (latanoprost) to lower IOP.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? • Yes / No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
Netarsudil-latanoprost contains two active substances: netarsudil, a protein kinase (ROCK) inhibitor, and latanoprost, an isopropyl ester prodrug.[1] These two components lower intraocular pressure (IOP) by increasing the outflow of aqueous humor (AH) via different mechanisms of action: the conventional (netarsudil) and unconventional (latanoprost) outflow. The combined effect of the two components results in additional IOP reduction compared to either compound administered alone.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Netarsudil-latanoprost is for ocular use only. If netarsudil-latanoprost is to be used concomitantly with other topical ophthalmic medicinal products, each medicinal product should be administered at least five minutes apart. Due to netarsudil's vasodilating properties, other eye drops should be administered before netarsudil-latanoprost. Eye ointments should be administered last. Contact lenses should be removed prior to instillation of netarsudil-latanoprost and may be reinserted 15 minutes following its administration. As with any eye drops, to reduce possible systemic absorption, it is recommended that the lachrymal sac be compressed at the medial canthus (punctal occlusion) for one minute. This should be performed immediately following the instillation of each drop. The tip of the dispensing container should avoid contacting the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. The recommended dosage is one drop in the affected eye(s) once daily in the evening. Patients should not instil more than one drop in the affected eye(s) each day. If one dose is missed, treatment should continue with the next dose in the evening. The fact that netarsudil-latanoprost is administered once daily will support patient adherence to treatment. The treatment is lifelong on a daily basis, provided patients meet the licensed indication.[1]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The evidence base of netarsudil-latanoprost for reducing elevated intraocular pressure (IOP) in adult patients with POAG or OHT for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction is provided in MERCURY 3, a phase III, double-blind, randomised controlled trial.[32]

The MERCURY 3 trial compared netarsudil-latanoprost with bimatoprost-timolol and enrolled subjects who were ≥18 years of age, with elevated IOP and a diagnosis of POAG or OHT.[32] The study was conducted between September 2017 (actual study start date) and November 2020 (actual primary completion) at 68 sites across 11 countries (Austria, Belgium, Czechia, France, Germany, Hungary, Italy, Latvia, Poland, Spain and the UK). A total of 430 subjects were enrolled and randomised in the trial (218 in the netarsudil-latanoprost group and 212 in the bimatoprost-timolol group). Adults with POAG or OHT, with a medicated IOP of ≥17 - <28 mmHg were included.

The primary efficacy outcome was mean IOP reduction between treatments through month 3. IOP measurements were taken using Goldmann applanation tonometry at 08:00, 10:00 and 16:00 at week 2, week 6 and month 3.

Secondary efficacy outcomes included mean change from diurnally adjusted baseline IOP at each post-treatment time point, and percentages of participants achieving pre-specified mean, mean change, and percent mean change in diurnal IOP levels.

In the safety assessment, IOP was measured at 10:00 at months 4, 5 and 6. Ocular adverse events (AEs) (side effects) and systemic safety assessments were made over 6 months.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Netarsudil-latanoprost demonstrated clinical non-inferiority versus bimatoprost-timolol for the primary endpoint in the intention-to-treat (ITT) population of the MERCURY 3 trial, in patients with POAG or OHT whose intraocular pressure (IOP) had not improved despite prior treatment.[32] The MERCURY 3 trial is the most robust source of evidence generalisable to the UK population for netarsudil-latanoprost.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Health-related quality of life (HRQoL) data was captured in the MERCURY 3 trial using the Short Form-36 (SF-36) questionnaire.[32] This instrument measures eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. SF-36 was measured in individuals in MERCURY 3 at screening and at study completion (month 6).

The SF-36 physical component (aggregate) scores, which provide a summary of the granular recordings from the MERCURY 3 trial show that the mean scores were broadly comparable between the netarsudil-latanoprost and bimatoprost-timolol treatment groups in the aggregate physical component score, with no statistical differences between the treatment arms. This is indicative of the SF-36 subscales, where little difference between the two arms was observed. Over the trial period, the values in the netarsudil-latanoprost arm marginally improved, whilst a marginal worsening was observed in the bimatoprost-timolol arm. Overall, patients in either treatment arm had similar perceptions of their general health at the different time points.

In a post hoc analysis of the intention to treat population (ITT) the results for the physical component summary showed that netarsudil-latanoprost had a considerable significant advantage in preventing a worsening of QoL in this group.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

In MERCURY 3, the safety profile of netarsudil-latanoprost was associated with reduced exposure compared to the bimatoprost-timolol group. Mostly mild to moderate ocular treatment-emergent adverse events (TEAEs) were observed, with no serious treatment-related TEAEs and no treatment-related deaths.[32]

The most common ocular adverse events (AEs) were conjunctival hyperaemia, cornea verticillata and conjunctival haemorrhage; a higher incidence of each of these AEs was observed in the netarsudil-latanoprost group compared to the bimatoprost-timolol group. The higher rate of hyperaemia experienced by patients in the netarsudil-latanoprost group may be due to the vasodilatory effect of the protein kinase (ROCK) inhibitors compared with the inflammatory allergic type typically experienced by bimatoprost-timolol patients.

It is important to note that the MERCURY 3 trial excluded patients who were known to be non-responders to bimatoprost-timolol or who showed insufficient tolerability to bimatoprost-timolol prior to entering the trial, thereby excluding such patients from the bimatoprost-timolol treatment group. This is a likely reason for the higher incidence of ocular AEs observed in the netarsudil-latanoprost treatment group compared to the bimatoprost-timolol group. A UK clinical expert advised that from a clinical perspective, the potential local and ocular side-effects of netarsudil-latanoprost (conjunctival hyperaemia, cornea verticillata and conjunctival haemorrhage) have limited clinical relevance. These local and ocular side-effects were considered as mild and manageable, particularly compared to systemic AEs.

Real-world data from the use of netarsudil-latanoprost in Germany has demonstrated that the rate of AEs is a lot lower in reality compared to what was observed in MERCURY 3.[33] Furthermore, the Committee for Medicinal Products for Human Use (CHMP) consider that the safety of netarsudil-latanoprost has been sufficiently demonstrated.[34]

Netarsudil-latanoprost is the only PGA-containing fixed-dose combination (FDC) treatment that does not contain a beta blocker. Beta blocker-containing ocular agents are associated with systemic side-effects and need to be cautiously prescribed in patients with contraindications, such as respiratory diseases and underlying cardiovascular conditions.[35] Therefore, netarsudil-latanoprost will provide an alternative treatment option for patients in whom beta-blockers are contraindicated or not tolerated. This could provide patients intolerant to beta blocker-containing ocular agents with an alternative treatment, that they could remain on for a lifetime duration, avoiding treatment switching.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

The trabecular meshwork (TM) is responsible for approximately 70-96% of aqueous humor (AH) outflow, which is one of the main mechanisms to control intraocular pressure (IOP).[18–20] Currently available topical treatments for glaucoma do not act directly on the TM to reduce IOP, highlighting an urgent unmet need. Netarsudil-latanoprost has a novel mechanism of action, as the first topical treatment for POAG/OHT that targets the TM pathway to increase AH outflow and hence reduce IOP. Additionally, only one drop of treatment needs to be applied in the affected eye(s) per day, which will support patient adherence to treatment compared to treatments requiring more than one drop daily.

Compared to bimatoprost-timolol, netarsudil-latanoprost demonstrated clinical non-inferiority in the intention-to-treat (ITT) population for the primary efficacy endpoint (mean IOP at specified time points at week 2, week 6 and month 3) in MERCURY 3. The safety profile of netarsudil-latanoprost was associated with reduced exposure compared to the bimatoprost-timolol group. Events were mostly mild to moderate ocular treatment-emergent adverse events (TEAEs), with no serious treatment-related TEAEs and no treatment-related deaths occurring.[32]

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

In MERCURY 3, the safety profile of netarsudil-latanoprost was associated with mostly mild to moderate ocular treatment-emergent adverse events (TEAEs), with no serious treatment-related TEAEs and no treatment-related deaths.[32]

The most common ocular adverse events (AEs) were conjunctival hyperaemia, cornea verticillata and conjunctival haemorrhage; a higher incidence of each of these AEs was observed in the netarsudil-latanoprost group compared to the bimatoprost-timolol group. Although the rate observed in the trial is higher than for some other medications or available fixed-dose combinations in the glaucoma field, it is of mild intensity.

The higher rate of hyperaemia experienced by patients in the netarsudil-latanoprost group may be due to the vasodilatory effect of the ROCK inhibitors compared with the inflammatory allergic type typically experienced by bimatoprost-timolol patients. Such irritation in real life is seen in patients with PGA drops and with other topical medications.

Real-world data from the use of netarsudil-latanoprost in Germany has demonstrated that the rate of AEs is a lot lower in reality compared to what was observed in MERCURY 3.[33] Furthermore, the Committee for Medicinal Products for Human Use (CHMP) consider that the safety of netarsudil-latanoprost has been sufficiently demonstrated.[34]

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Netarsudil-latanoprost is a step change in the clinical management of POAG and OHT in patients who are currently underserved by existing treatment options. As such, the company performed an economic analysis to assess the cost-effectiveness of netarsudil-latanoprost vs. fixed-dose combinations (FDC) in adult patients with POAG or OHT for whom monotherapy (one single treatment) with a prostaglandin or netarsudil provides insufficient reduction in intraocular pressure (IOP) (fluid pressure of the eye).

The economic model was based on health states defined by percentage reductions in IOP, as this is considered a clinically relevant treatment outcome for patients with POAG/OHT as indicated by United Kingdom (UK) clinical experts. IOP reductions indicate an improvement in condition. Clinical parameters for the model were informed by the MERCURY 3 trial and outputs from an indirect treatment comparison (ITC), which was conducted to gather comparative evidence for netarsudil-latanoprost vs. FDC comparators for which head-to-head data was not available. In the absence of long-term treatment effectiveness data, extrapolations (estimations beyond the period for which data were available) were applied which were informed by taking an average of the clinical parameters from the early stages of the model for which data was available. The 36-item Short Form Survey (SF-36) data from the MERCURY 3 trial was mapped to the EuroQol

5-dimension (EQ-5D) to inform quality of life in the model, which showed that the quality of life of patients improves as reductions in IOP are observed – that is, as the condition improves. A reduction in quality of life due to experiencing adverse events (AEs) was also incorporated in the model for each treatment. The quality of life of caregivers for patients with POAG/OHT was not included in the model as per UK clinical expert input. Sensitivity analyses were conducted to test uncertainty in the model.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Netarsudil-latanoprost has a novel mechanism of action, as the first topical treatment for POAG/OHT that targets the trabecular meshwork (TM) pathway to increase aqueous humor (AH) outflow and hence reduce intraocular pressure (IOP). The TM is responsible for approximately 70-96% of AH outflow, which is one of the main mechanisms to control IOP.[18–20] Currently available topical treatments for glaucoma do not act directly on the TM to reduce IOP, highlighting an urgent unmet need for a treatment like netarsudil-latanoprost which does so.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Glaucoma risk differs between ethnic groups.[36] There is not sufficient evidence to support separate evaluations of the clinical effectiveness and cost-effectiveness of netarsudil-latanoprost for separate ethnic groups.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on POAG/OHT and getting involved with a patient group:

- NHS website for glaucoma: https://www.nhs.uk/conditions/glaucoma/
- NICE guideline for glaucoma: https://www.nice.org.uk/guidance/ng81
- Glaucoma UK website: https://glaucoma.uk/
- Information on understanding glaucoma generally: https://glaucoma.uk/about-glaucoma/what-is-glaucoma/
- Information on understanding OHT generally: https://glaucoma.uk/ocular-hypertension/

- Information on netarsudil-latanoprost specifically:
- Summary of product characteristics: Microsoft Word - 358609949878436016l_spc-doc.doc (windows.net)
- Mercury 3 Poster egs2022-prog-0531.pdf page 34 (Awaiting full publication of MERCURY 3)

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

AE	Adverse event
AH	Aqueous humor
BB	Beta-blocker
CAI	Carbonic anhydrase inhibitors
EGS	European Glaucoma Society
EMA	European Medicines Agency
EQ-5D	EuroQol 5-dimension
EVP	Episcleral venous pressure
FDC	Fixed-dose combination
HRQoL	Health-related quality of life
IOP	Intraocular pressure
ITC	Indirect treatment comparison
ITT	Intention-to-treat
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OHT	Ocular hypertension
OHTS	Ocular Hypertension Treatment Study
PGA	Prostaglandin analogue
POAG	Primary open-angle glaucoma
RNFL	Retinal nerve fibre layer
ROCK	Rho-(associated) coiled-coil containing protein kinase inhibitor
SLT	Selective laser trabeculoplasty
SF-36	36-item Short Form Survey

TEAE	Treatment-emergent adverse event
TM	Trabecular meshwork
UK	United Kingdom

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Roclanda (netarsudil-latanoprost) summary of product characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/roclanda-epar-product-information_en.pdf. Last accessed: March 2023.

2. Mahabadi N, Foris LA, Tripathy K. Open Angle Glaucoma. [Updated 2022 Aug 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441887/.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Netarsudil-latanoprost for previously treated open-angle glaucoma or ocular hypertension [ID1363]

Clarification questions

October 2023

File name	Version	Contains confidential information	Date
		Yes/no	

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Systematic literature review

A1. Document B, section B.2.5, page 40; and Appendix D.4, page 75. These sections of the company submission refer to the quality assessment of the MERCURY 3 study and other studies identified in the SLR. Please clarify how many reviewers carried out the risk of bias assessment of these studies and whether they worked independently.

One reviewer independently carried out the risk of bias assessment, which was then quality checked by a second reviewer. Any discrepancies were discussed, and a third reviewer involved if necessary to reach a decision.

A2. PRIORITY Appendix D, Tables 1-4. The dates for the literature searches are 2017 to 2022, but no reason for this cut-off is given in Document B or Appendix D: please explain why these dates were chosen. We believe that relevant pre-2017 studies are available and should be included.

In the initial systematic literature review (SLR) database searches conducted for this appraisal, no date restriction was applied, however this yielded a large number of hits across all treatments for primary open-angle glaucoma (POAG) / ocular hypertension (OHT) included in the NICE scope for netarsudil-latanoprost. As the SLR conducted

as part of NG81 was conducted in 2017, this was deemed a reasonable cut-off to search from. Therefore, a five-year date restriction was applied to ensure that only the most recent evidence was selected for use in the submission.

This said, as agreed during the clarification question call with the External Assessment Group (EAG) on 26th July 2023, targeted searches to identify relevant pre-2017 studies have now been conducted (rather than a formal systematic literature review), due to the appraisals focus on FDC comparators. As described in Table 51 of Appendix A, and the aforementioned statement on the availability of FDC evidence, most FDC studies are recent, and due to the time and resource constraints faced through re-running the full SLR using FDCs only, it was agreed that a TLR was an appropriate substitution for the standard SLR approach.

For the targeted database searches, the original SLR search terms (see Appendix D of the original submission dossier) were reviewed and refined in response to Questions A5 and A6 below. Since it is expected that the NICE recommended population will reflect the license wording for netarsudil-latanoprost and will be limited to adult patients with POAG or OHT for whom monotherapy (with a prostaglandin or netarsudil) provides insufficient IOP reduction,[1] the intervention/comparator search terms were limited to the expected comparators within this population (FDC therapies), i.e., search terms for monotherapies were removed. The search strategies for the targeted database searches are detailed in Appendix A (Table 51, Table 52, Table 53, Abbreviations: HRQoL – health-related quality of life

Table *54*, Abbreviations: NHS – national health service; EED – economic evaluation database; HTA – health technology assessment; QoL – quality of life

Table *55*, Abbreviations: HRQoL – health-related quality of life; ScHARRHUD - School of Health and Related Research Health Utilities Database

Table *56*, Table 57) of this document.

Targeted searches were conducted in the following databases for all time up to 2017: Embase, Cochrane Central Register of Controlled Trials (Cochrane library), Cochrane Clinical Answers, CRD Health Technology Assessment (HTA) Database (1989 to present), CRD National Health Service (NHS) Economic Evaluation Database (EED)

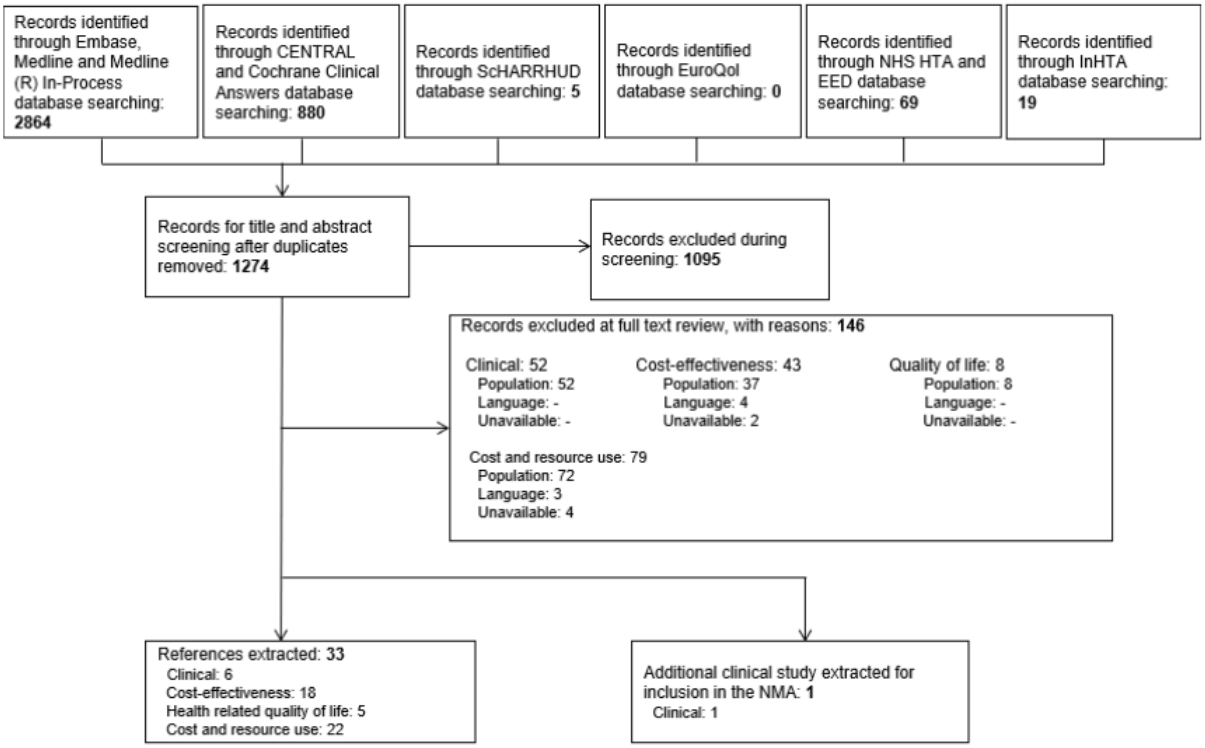
(from 1994 and March 2015), University of Sheffield School of Health and Related Research Health Utilities Database (ScHARRHUD) (2010 to present) and the EuroQol database (1970 to present). Additionally, in line with Question A3 below, the International HTA Database was searched from 2015 to 2022 to comprehensively identify more recent HTAs and/or cost-effectiveness studies. It should be noted that this database is partially captured by the CRD interface. This database is recommended on the University of York Centre for Reviews and Dissemination (CRD) website.[2]

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram in Figure 1 below summarises the screening of publications through each stage of the targeted database searches, including both the clinical and economic searches.

The database searches retrieved 3,837 references. Among these, there were a total of 2,563 duplicates, which when removed resulted in 1,274 unique references eligible for screening.

Of the 1,274 titles and abstracts screened with the eligibility criteria, a total of 1,241 references (1,095 at screening and 146 at full text review) were excluded, resulting in 33 unique references eligible for data extraction.

Figure 1: PRISMA diagram for targeted searches



Abbreviations: EED – economic evaluation database; HTA – health technology assessment; InHTA – international health technology assessment; NHS – National Health Service; PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ScHARRHUD – School of Health and Related Research Health Utilities Database

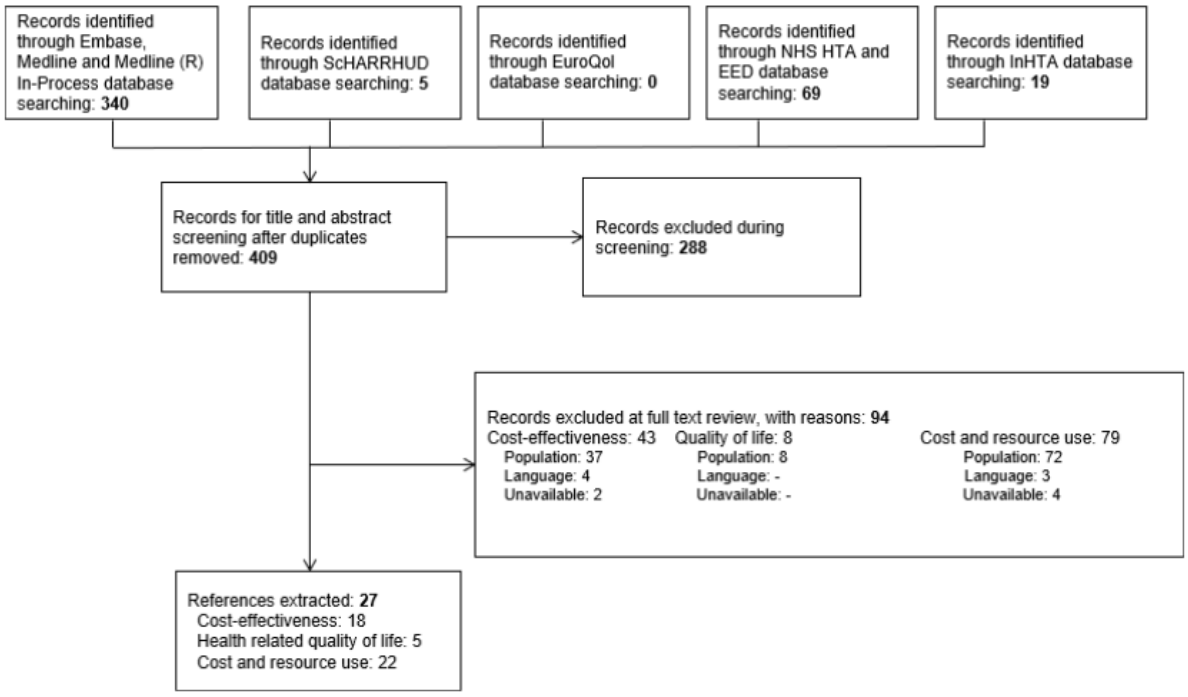
Details of the clinical, cost-effectiveness and HRQoL studies identified from the targeted database searches can be found in the responses to Question A8, Question B1, and Question B12, respectively. The results of the cost and resource use studies are detailed below.

Figure 2 summarises the screening of economic publications through each stage of the targeted database searches. The economic searches retrieved 433 hits. After removing 24 duplicates, 409 references were eligible for title and abstract screening. 121 unique references met the criteria for the full text review stage. Following the review of full texts, a total of 94 publications were excluded as they did not meet the selection criteria, leaving a total of 27 publications. Of this total, 22 publications met the selection criteria for the cost and resource use review question, and data were extracted.

Please see Table 67, Table 68,

Table ***69***, Table 70, and Table 71 in Appendix A of this document for a summary of the cost and resource use publications identified as part of the targeted searches.

Figure 2: PRISMA for economic studies targeted database searches



Abbreviations: EED – Economic Evaluation Database; HTA – Health technology assessment; InHTA – International Health Technology Assessment; NHS – National Health Service; PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ScHARRHUD – School of Health and Related Research Health Utilities Database

A3. Appendix D. Table 3, page 26. The NHSEED and HTA databases were searched using the CRD interface from 2017 onwards, but these databases have had no new records added since the end of 2015. Please explain what steps were taken to comprehensively identify more recent HTAs and/or cost-effectiveness studies.

The International HTA Database (INAHTA) provides access to information about ongoing and published health technology assessments commissioned or undertaken by HTA organisations around the world. This database was not previously searched in the original SLR, but has now been searched as part of the targeted database searches. This database is recommended on the University of York Centre for Reviews and Dissemination (CRD) website.[2]

The search strategy for the INAHTA database and the number of hits are detailed in Table 57, in Appendix A of this document. The hits identified from this database (19) were combined with the hits identified from the remaining database searches before being screened. The company believe that by performing additional searches in the INAHTA database, all evidence of interest has now been included in the submission. See Question A2 for details on the number of hits from the INAHTA database and Question B1 for cost-effectiveness study results.

A4. PRIORITY Appendix D, Section D.2 Search strategies. Only Embase was searched, which includes MEDLINE content indexed using Embase Emtree. Current recommendations are that MEDLINE should be searched separately using its own MeSH indexing to ensure a comprehensive search. We are of the opinion that a MEDLINE search should be carried out.

Embase contains the following three databases: the Embase database, the MEDLINE database and Embase Classic.[3] Therefore, the company considers that a separate search in MEDLINE is not required as searches in Embase are comprehensive and include MEDLINE journals from 1966 to present.

Furthermore, as agreed during the clarification question call with the External Assessment Group (EAG) on 26th July 2023, targeted searches have been performed for evidence pre-2017 rather than performing a formal SLR update, therefore searching Embase alone is sufficient for this purpose.

A5. PRIORITY Appendix D, Section D.2 Search strategies. The Embase search includes the phrase "randomi*ed controlled trial" but this does not identify similar phrases such as 'randomised clinical trial' (as evidenced by the failure to identify the recent Cochrane review by Freiberg et al., 2022 on this clinical topic). We are concerned that the search strategy is not sensitive enough and might have missed relevant publications. We recommend that the search strategy is reformulated and rerun.

The company can confirm that the Cochrane review by Freiberg *et al.* 2022 was identified in the original SLR. However, in line with the inclusion and exclusion criteria of the SLR (see Table 6 in the Appendices D.2.1 of the original submission), this publication was excluded at first pass screening because it is a review. Hence, the company believe that the original SLR search strategy was sensitive enough to identify all relevant publications. Furthermore, as agreed during the clarification question call with the External Assessment Group (EAG) on 26th July 2023, targeted searches have been performed for evidence pre-2017 rather than performing a formal SLR update, therefore a reformulation and rerun of the search strategy is not required.

As previously outlined in response to Question A2, the original SLR search terms (see Appendix D of Document B) were reviewed and refined in response to Questions A5 and Question A6 when running the targeted database searches. The search strategies for the targeted database searches are detailed in Table 51 and Table 52 Appendix A of this document. Updates made in line with Questions A5 and A6 are in bold.

A6. Appendix D, Section D.2 Search strategies. The searches of the different databases are not equivalent; the Embase search includes the terms ‘open-angle glaucoma’, ‘ocular hypertension’ and ‘glaucoma’ but the CENTRAL search only uses the term ‘open-angle glaucoma’ so appears to be less comprehensive. We recommend that the search strategies are reformulated and rerun to achieve equivalence across databases.

In the updated targeted database searches as detailed in Question A2, the search strategies for the databases have been updated to ensure alignment across the databases. The updated search strategies are provided in Appendix A of this document. Modifications made, including those to the population terms to ensure that the database searches are equivalent, are in bold.

A7. Appendix D2.3, Table 7, pages 33-34, and Appendix D2.4, Table 8, pages 35-63. For each study excluded from the indirect treatment comparisons (Table 7), please clarify the reason for exclusion. Please clarify how many of the studies in Tables 7 and 8 would have been eligible for inclusion in an evidence synthesis (e.g., a network meta-analysis) according to the original NICE scope.

Only studies that passed the SLR screening and had data extracted were assessed for inclusion in the ITC i.e., Table 7 and Table 8 (in Document B) studies were included and excluded from the SLR, respectively, which also applied for the ITC.

As discussed in Table 1 and Section 2.9.1.1 of Document B, to reflect the license wording and NICE recommended population, evidence in the submission including the indirect treatment comparison was limited to 'adult patients with POAG or OHT for whom monotherapy with a PGA or netarsudil provides insufficient IOP reduction' (i.e., those eligible for treatment with FDCs).[4] In accordance with this and as alluded to in Section 2.9.1.1 of Document B, studies in Table 7 were only assessed for inclusion in the ITC if they included an FDC as a standalone comparator. Furthermore, it was agreed during the clarification question call with the External Assessment Group (EAG) on 26th July 2023, that studies containing monotherapies only would only be included in the ITC if they would create a connected network between FDC-containing studies.

Indirect treatment comparisons

A8. PRIORITY. Document B, section B.2.9. Although we understand that the company changed the scope due to the marketing authorisation, we believe that it might still be possible to conduct a network meta-analysis including both monotherapies and combination therapies to link different combination therapies. This would allow for a more comprehensive assessment of current evidence and would be clinically relevant. We are also concerned that the MAIC/STC methods have strong assumptions that are difficult to justify. We recommend considering conducting such network meta-analysis and using its outputs to populate the economic model.

Targeted database searches

As detailed in the response to Question A2, targeted searches were conducted for clinical studies for all time up to 2017 in response to the EAG clarification questions. The aim was to identify any pre-2017 FDC clinical studies that met the SLR criteria and update the network of evidence from the original submission with the objective of conducting a network meta-analysis (NMA). If such an NMA was found to be feasible, the output of the NMA would replace the current MAIC and STC comparative efficacy estimates applied in the CEM.

The PRISMA diagram in Figure 1 (Question A2) summarises the screening of publications through each stage of the targeted database searches. As described in the PRISMA, 865 unique references met the criteria for the full text review stage. Following the review of full texts, a total of 807 publications were excluded as they did not meet the selection criteria, leaving 52 publications. Of these 52 publications, six publications met the selection criteria for the clinical review and were extracted.

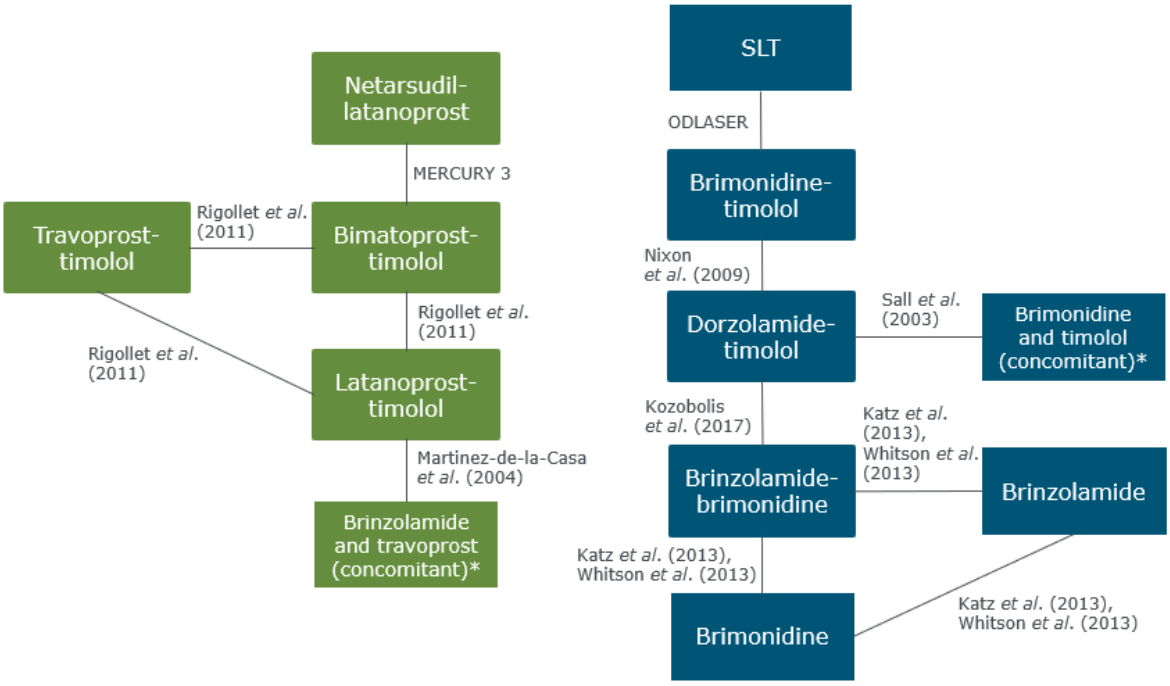
Please see Table in Appendix A of this document for a summary of the FDC clinical publications extracted as part of the targeted searches.

Summary of trials included in the indirect treatment comparison

Detailed in Section B.2.9.1.2 of the original submission, three relevant FDC clinical studies were identified in the SLR and were considered feasible for inclusion in the ITC (MERCURY 3, ODLASER and Kozobolis *et al*. [2017]).[5–7] The updated targeted database searches identified a further six relevant studies that included an FDC as an intervention or comparator.[8–13]

The network of evidence for netarsudil-latanoprost and FDCs, based on a total of nine RCTs identified collectively from the original SLR and updated targeted database searches, is presented in Figure 3. [5–13]

Figure 3: Updated evidence network, including the FDC clinical studies identified from the targeted database searches

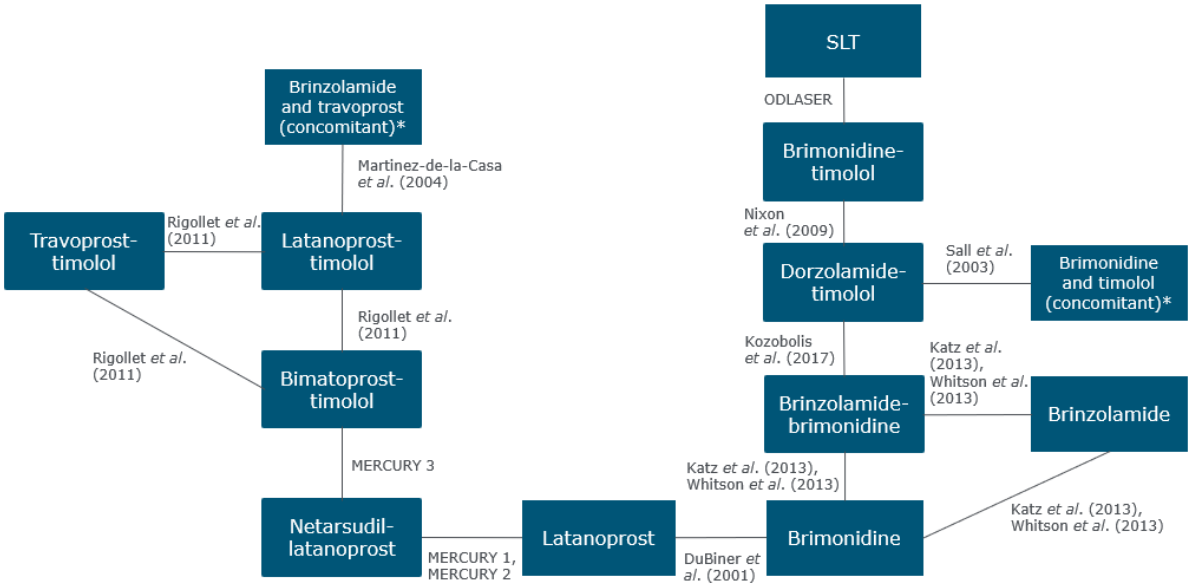


Abbreviations: FDC – Fixed-dose combination; SLT – Selective laser trabeculoplasty
*Concomitant use (not an FDC)

The updated evidence network formed two disjoint networks. It was agreed during the clarification question call with the EAG on 26th July 2023 that monotherapies could be included in the evidence network to connect the FDC comparators if appropriate (but only for this reason). Therefore, the inclusion of monotherapy studies to bridge the two networks was explored.

Potential solutions to bridge the network were explored using the monotherapy studies previously identified and extracted in the original SLR. Additionally, the targeted database search hits were re-screened to identify relevant monotherapy studies that could bridge the two networks. It was determined that a connected network could be formed by introducing one monotherapy comparator into the network. A bridge was formed between netarsudil-latanoprost and brimonidine using three studies including latanoprost; the MERCURY 1 and MERCURY 2 RCTs (which had been identified as part of the original SLR) compared latanoprost with netarsudil-latanoprost,[14,15] and DuBiner *et al*. (2001); which had been identified during the updated targeted database searches) compared latanoprost with brimonidine.[16] The connected network, bridged with latanoprost, is presented in Figure 4.

Figure 4*:* Connected evidence network



Abbreviations: FDC – Fixed-dose combination; SLT – Selective laser trabeculoplasty
*Concomitant use (not an FDC)

An external statistical expert advised that the following studies should be removed from the network since they do not provide a feedback loop and hence, excluding them would not change the comparative efficacy estimates: Sall *et al*. (2003), Martinez de-la-Casa *et al*. (2004) and ODLASER.[7,9,11] The final restricted network of nine RCTs that were assessed for feasibility of inclusion in the NMA is presented in Figure 5. The nine studies included in the network for assessment are summarised in

Table ***1***.

Figure 5: Restricted evidence network for assessment

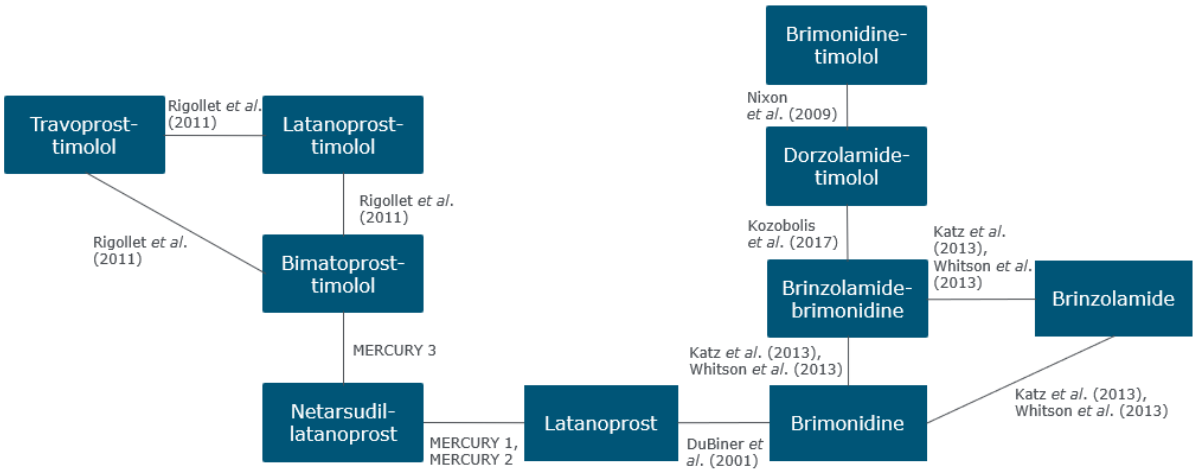


Table 1: Summary of the relevant studies identified for assessment

Trial name	Intervention(s)	Study design	IOP endpoints
DuBiner *et al*. (2001)[16]	Arm 1: Brimonidine (64) Arm 2: Latanoprost (61)	Multicentre, double-blinded, parallel-group clinical trial. Based in the US.	Mean IOP and mean change in IOP at month 1 and month 3
Nixon *et al*. (2009)[10]	Arm 1: Brimonidine-timolol (91) Arm 2: Dorzolamide-timolol (89)	Randomised, parallel-group, observer-masked clinical trial. Based in the US.	Mean IOP at month 3
Rigollet *et al*. (2011)[8]	Arm 1: Latanoprost-timolol (42) Arm 2: Bimatoprost-timolol (44) Arm 3: Travoprost-timolol (44)	Randomized, prospective, single-blind study. Based in Spain.	Absolute decrease in IOP at month 1, month 2, month 3, month 4, month 5, month 6, and month 12
Katz *et al*. (2013)[12]	Arm 1: Brinzolamide-brimonidine (209) Arm 2: Brinzolamide (224) Arm 3: Brimonidine (216)	Phase 3, double-masked, parallel-group, multicentre study. Based in the US.	Mean IOP at specified time points at week 2, week 6, and month 3
Whitson *et al*. (2013)[13]	Arm 1: Brinzolamide-brimonidine (218) Arm 2: Brinzolamide (229) Arm 3: Brimonidine (232)	Phase 3, randomised, double-blinded, multicentre, parallel-group study. Based in the US.	Mean IOP at week 2 and month 3, percentage reduction in IOP from baseline to month 6, absolute IOP reduction from baseline to month 6
Kozobolis *et al*. (2017)[5]	Arm 1: Brinzolamide-brimonidine (22) Arm 2: Dorzolamide-timolol (22)	Prospective, randomised, double-blinded, parallel-group. Based in Greece.	IOP at specified time points (morning and afternoon) at week 1, week 4, week 8 and week 12
MERCURY 1[14]	Arm 1: Netarsudil-latanoprost (238) Arm 2: Netarsudil (244)* Arm 3: Latanoprost (236)	Double-blinded, randomised, multicentre, active-controlled, parallel-group, phase 3, study. Based in 56 active sites in 23 states across the US.	Mean IOP and mean diurnal IOP at week 2, week 6, month 3, month 9, month 12, and month 13 (off treatment extension period)
MERCURY 2[15]	Arm 1: Netarsudil-latanoprost (245) Arm 2: Netarsudil (255)* Arm 3: Latanoprost (250)	Prospective, double-blinded, randomised, multicentre, active-controlled, parallel-group trial. Based in 60 active sites in the US and Canada.	Mean IOP and mean percentage change in IOP at week 2, week 6, and month 3
MERCURY 3[6]	Arm 1: Netarsudil-latanoprost (n=218) Arm 2: Bimatoprost-timolol (n=212)	Prospective, double-blinded, randomised, multicentre, active-controlled, parallel-group, phase 3 trial.	Mean IOP at specified time points at week 2, week 6 and month 3

		Based across 11 countries.	

Abbreviations: IOP – Intraocular pressure; US – United States
*Treatment arm not included in the assessment – monotherapy does not bridge the network.

NMA feasibility assessment overview

The suitability of trials for inclusion in the NMA was determined by assessing whether they were sufficiently homogeneous. Australian Pharmaceutical Benefits Advisory Committee (PBAC) guidance was used to assess the level of heterogeneity across studies by comparing study designs, population characteristics, treatment arms and outcomes.[17] Assessing heterogeneity between studies should take account of key features of the studies such as those listed in Table 2. These features have been adapted so that they are relevant to our assessment of treatments for POAG or OHT.

Table 2: Examples of factors that might cause heterogeneity

Category	Factor
Different quality or methods of randomised trials	• Design • Adequate concealment of randomisation • Blinding • Duration of follow-up • Loss to follow-up • Inclusion and exclusion criteria
Confounding factors in relation to participant population	• Age • IOP • Visual field mean deviation • Corneal thickness • Family history of glaucoma • Cup-to-disc ratio • Disc haemorrhages • Baseline visual field indices • Retinal nerve fibre layer • Corneal hysteresis
Confounding factors in relation to circumstances	• Date of study • Geography
Different treatment	• Treatment administration • Dose • Duration • Timing
Different outcome measures and methods of statistical analysis	• Definition of outcome(s) • Rating instrument • Frequency of measurement

	• Start point of measurement against duration or progression of disease or treatment, especially in time-to-event analyses • Availability of data

Abbreviations: IOP – Intraocular pressure

Study design heterogeneity

The study design of the nine RCTs considered in the NMA feasibility assessment are shown in Table 81 and Table 82 of Appendix B.

All RCTs recruited patients diagnosed with POAG or OHT,[6,8,10,12–16] except for Kozobolis *et al.* (2017) which only included POAG patients.[5] Five studies (Katz *et al.* [2013], Whitson *et al.* [2013], MERCURY 1, MERCURY 2, MERCURY 3) were Phase 3 RCTs while the remaining studies did not report the trial phase.[6,12–15] Many of the RCTs were multicentred (DuBiner *et al.* [2001], Katz *et al.* [2013], Whitson *et al.* [2013], MERCURY 1, MERCURY 2, MERCURY 3).[6,12–16]

DuBiner *et al.* (2001), Katz *et al.* (2013), Whitson *et al.* (2013), Kozobolis *et al.* (2017), MERCURY 1, MERCURY 2, and MERCURY 3 were double-blinded RCTs,[5,6,12–16] while Nixon *et al.* (2009) and Rigollet *et al.* (2011) were single-blinded studies.[8,10] The duration of follow-up for the RCTs ranged from 3 months to 12 months. As for randomisation, several studies utilised a computer generated randomisation schedule (Nixon *et al.* [2009], Rigollet *et al.* [2011], MERCURY 1)[8,10,14] or an investigator carried out randomisation (DuBiner *et al.* [2001], MERCURY 2, MERCURY 3).[6,15,16] Katz *et al.* (2013) conducted randomisation by an interactive web responses system,[12] while Whitson *et al.* (2013) and Kozobolis *et al.* (2017) did not report randomisation methods.[5,13]

In summary, minimal variation in study design existed between studies. As such, no studies were excluded due to study design heterogeneity.

Patient population heterogeneity

The baseline characteristics of the nine RCTs considered in the NMA feasibility assessment are summarised in Table 83 and Table 84 of Appendix B.

All RCTs, except for Katz *et al.* (2013) who did not report the trial's inclusion and exclusion criteria, were aligned on inclusion and exclusion criteria surrounding age, with patients aged 18 years or older eligible for study participation.[5,6,8,10,13–16] Across the nine trials and all treatment arms, the mean baseline age varied minimally between 61 years and 71 years.[10,16]

Eight studies explicitly reported the study eye diagnosis of patients and included both OAG and OHT patients in the trial, except for Kozobolis *et al*. (2017) which only included patients with POAG reflecting the eligibility criteria for both studies.[6,8,10,12–16]

Across the trials that reported mean diurnal IOP at baseline (DuBiner *et al.* [2001], Rigollet *et al.* [2011], Whitson *et al.* [2013], Kozobolis *et al.* [2017], MERCURY 1, MERCURY 2, MERCURY 3), mean diurnal IOP at baseline varied minimally between 23.5 mmHg and 28.2 mmHg.[5,14] Mean IOP at screening for the study eye was only reported in Katz *et al.* (2013), Nixon *et al.* (2009), and MERCURY 3, and varied minimally with a range of 20.5 mmHg to 27.1 mmHg.[6,12]

Only MERCURY 3 reported the cup-to-disc ratio of patients at baseline.[6] This was 0.48 for patients in both treatment arms.

Most RCTs reported previous treatment in patients. There was some variation in the proportion of patients who were treatment naïve or previously treated across the trials. DuBiner *et al.* (2001) included 39.4% and 47.5% treatment naïve patients in the brimonidine and latanoprost treatment arms respectively,[16] in contrast to MERCURY 3 where all patients had previously been treated with a combination therapy, prostaglandins, or other monotherapies.[6] Similarly, Kozobolis *et al.* (2017) included 45.5% treatment naïve patients in the brinzolamide-brimonidine arm, and 40.9% treatment naïve patients in the dorzolamide-timolol arm.[5] However, since previous treatment was not validated as a key effect modifier or prognostic variable by a UK clinical expert,[18] the difference in previous treatments between trials was not expected to cause bias in the NMA results.

In summary, the variation in patient population that existed between studies was largely minimal. Only previous treatment greatly differed between studies. However, this was not expected to result in bias in the NMA since previous treatment was not identified as a key treatment effect modifier by a UK clinical expert,[18] (see section B.2.9.1.3 in Document B of the original submission). Therefore, no studies were excluded due to patient population heterogeneity.

Treatment arm heterogeneity

For treatments that have been assessed in multiple studies, it was necessary to compare how these treatments had been administered in the different trials to assess

whether the anchor treatment arms were sufficiently homogeneous. Treatments which were informed by only one study did not need to be compared as they will not be compared across studies. The following comparators were considered: netarsudil-latanoprost, latanoprost, brimonidine, brinzolamide-brimonidine, brinzolamide and dorzolamide-timolol. For these treatments, the treatment dose and administration process, duration of treatment and the frequency of administration (timing) was considered.

Comparability of netarsudil-latanoprost

The dose and administration schedule of netarsudil-latanoprost across the MERCURY trials are compared in Table 3. The dose administration and regimen were equivalent. Treatment duration varied between three months and 12 months. However, IOP efficacy data was reported at three months for each study, and therefore efficacy data at an equal treatment duration of three months could be used in the analysis.

Table 3: Comparability of netarsudil-latanoprost treatment arms

Trial	Dose	Administration	Duration of treatment	Timing
MERCURY 1[14]	Netarsudil 0.02%/latanoprost 0.005%	Eye drop	12 months	Once daily (between 8:00PM and 10:00PM)
MERCURY 2[15]	Netarsudil 0.02%/latanoprost 0.005%	Eye drop	3 months	Once daily (PM)
MERCURY 3[6]	Netarsudil 0.02%/latanoprost 0.005%	Eye drop	6 months	Once daily (between 8:00PM and 10:00PM)

Comparability of latanoprost

The dose and administration schedule of latanoprost across the MERCURY 1, MERCURY 2 and DuBiner *et al*. (2001) trials are compared in Table 4. Across all trials, the latanoprost dose was equivalent and administered in the evening. In MERCURY

1 and MERCURY 2, one drop of latanoprost was administered per day. Marginal variation existed in comparison to DuBiner *et al*. (2001), where between one and two drops were administered per day. Treatment duration varied between three months and 12 months. However, IOP efficacy data was reported at three months for each study, and therefore efficacy data at an equal treatment duration of three months could be used in the analysis.

Table 4: Comparability of latanoprost treatment arms

Trial	Dose	Administration	Duration of treatment	Timing
MERCURY 1[14]	Latanoprost 0.005%	Eye drop	12 months	One drop once daily (between 8:00PM and 10:00PM)
MERCURY 2[15]	Latanoprost 0.005%	Eye drop	3 months	One drop once daily (between 8:00PM and 10:00PM)
DuBiner *et al*. (2001)[16]	Latanoprost 0.005%	Eye drop	3 months	One or two drops (between 7:00 and 9:00AM) and one or two drops (between 7:00 and 9:00PM)

Comparability of brimonidine

The dose and administration schedule of brimonidine across the DuBiner *et al*. (2001), Katz *et al*. (2013) and Whitson *et al*. (2013) trials are compared in Table 5. The dose and regimen were equivalent in Katz *et al*. (2013) and Whitson *et al*. (2013) – brimonidine was administered three times daily.[12,13] Meanwhile, variation existed in the dose timing in DuBiner *et al*. (2001) where one or two drops of brimonidine were administered twice daily.[16] Treatment duration varied between three months and six months. However, IOP efficacy data was reported at three months for each study, and

therefore efficacy data at an equal treatment duration of three months could be used in the analysis.

Table 5: Comparability of brimonidine treatment arms

Trial	Dose	Administration	Duration of treatment	Timing
DuBiner *et al*. (2001)[16]	Brimonidine 0.2%	Eye drop	3 months	One or two drops (between 7:00 and 9:00 AM) and one or two drops (between 7:00 and 9:00PM)
Katz *et al*. (2013)[12]	Brimonidine 0.2%	Eye drop	3 months	Three times daily (at 8:00 AM, 3:00 PM, and 10:00 PM (+/-30 minutes))
Whitson *et al*. (2013)[13]	Brimonidine 0.2%	Eye drop	6 months	Three times daily (at 8:00 AM, 3:00 PM, and 10:00 PM (+/-30 minutes))

Comparability of brinzolamide-brimonidine

The dose and administration schedule of brinzolamide-brimonidine across the Katz *et al*. (2013), Whitson *et al*. (2013) and Kozobolis *et al*. (2017) trials are compared in Table 6.

The dose administration and regimen were equivalent in Katz *et al*. (2013) and Whitson *et al*. (2013).[12,13] However, variation existed in the frequency of administration in Kozobolis *et al*. (2017) (twice daily rather than three times daily as in Katz *et al*. [2013] and Whitson *et al*. [2013]).[12,13] In the literature, recommendations permit the use of brinzolamide-brimonidine two to three times daily.[19–21] Additionally, the dose

frequency in each of the trials is consistent with the dosing regimen recommended for the study location. For instance, Whitson *et al*. (2013) and Katz *et al*. (2013) were conducted in the US and therefore, a three-times daily dose aligns with the Novartis prescribing information whereas Kozobolis *et al*. (2017) was conducted in Greece and therefore a twice-daily dose aligns with EMA Summary of Product Characteristics (SmPC). For this reason, it was not necessary to exclude any of the three studies from the NMA. Treatment duration varied between three months and six months. However, IOP efficacy data was reported at three months for each study, and therefore efficacy data at an equal treatment duration of three months could be used in the analysis.

Table 6: Comparability of brinzolamide-brimonidine treatment arms

Trial	Dose	Administration	Duration of treatment	Timing
Katz *et al*. (2013)[12]	Brinzolamide 1.0%/ brimonidine 0.2%	Eye drop	3 months	3 times daily (at 8:00AM, 3:00 PM, and 10:00 PM (+/-30 minutes))
Whitson *et al*. (2013)[13]	Brinzolamide 1.0%/ brimonidine 0.2%	Eye drop	6 months	3 times daily (at 8:00 AM, 3:00 PM, and 10:00 PM (+/-30 minutes))
Kozobolis *et al*. (2017)[5]	Brinzolamide 1.0%/ brimonidine 0.2%	Eye drop	3 months	Twice daily

Comparability of brinzolamide

The dose and administration schedule of brinzolamide across the Katz *et al*. (2013) and Whitson *et al*. (2013) trials are compared in Table 7. The dose administration and regimen were equivalent. Treatment duration varied between three months and six months. Additionally, IOP efficacy data was reported at three months for each study,

and therefore efficacy data at an equal treatment duration of three months could be used in the analysis.

Table 7: Comparability of brinzolamide treatment arms

Trial	Dose	Administration	Duration of treatment	Timing
Katz *et al.* (2013)[12]	Brinzolamide 1.0%	Eye drop	3 months	3 times daily (at 8:00 AM, 3:00 PM, and 10:00 PM (+/-30 minutes))
Whitson *et al.* (2013)[13]	Brinzolamide 1.0%	Eye drop	6 months	3 times daily (at 8:00 AM, 3:00 PM, and 10:00 PM (+/-30 minutes))

Comparability of dorzolamide-timolol

The dose and administration schedule of dorzolamide-timolol across the Nixon *et al.* (2009) and Kozobolis *et al.* (2017) trials are compared in Table 8. The dose, administration, timing and treatment duration were equivalent.

Table 8: Comparability of dorzolamide-timolol treatment arms

Trial	Dose	Administration	Duration of treatment	Timing
Nixon *et al.* (2009)[10]	Dorzolamide 2%/ Timolol 0.5%	Eye drop	3 months	Twice daily (Between 7:00 AM and 8:00 AM, between 7:00 PM and 8:00 PM)
Kozobolis *et al.* (2017)[5]	Dorzolamide 2%/ Timolol 0.5%	Eye drop	3 months	Twice daily

In summary, minimal variation existed between treatment arms and as such, no studies were excluded due to treatment arm heterogeneity.

Outcome measure heterogeneity

Consistent with the previous ITC analyses conducted, the outcome of interest for the NMA was the percentage change in diurnal IOP from baseline. Justification of the inclusion of this endpoint is detailed in Section B.2.9.1.2.1 in Document B of the original submission.

In the previous analyses, the feasibility of conducting an NMA for two additional outcomes was also considered (discontinuation and incidence of treatment-emergent adverse events [TEAEs]). Analyses for these outcomes were deemed unfeasible due to a lack of reported data, and hence, discontinuation rates and incidences of TEAEs were sourced from the literature accordingly. These sources were considered sufficient to negate the need to assess these two endpoints in the updated NMA.

An overview of IOP available data from the nine trials considered in the NMA feasibility assessment is presented in Table 9. For all studies considered, IOP data was reported at baseline and a 3-month time point. Therefore, the NMA analyses were based on change from baseline in IOP data after 3 months on treatment. In all nine RCTs, sufficient data was reported to simulate percentage change from baseline in diurnal IOP (Table 72 to Table 82 in Appendix B). Rigollet *et al*. (2011) did not report standard deviations for the baseline IOP values and mean IOP values at three months; therefore, it was assumed that the standard deviations (SD) of mean IOP at baseline and 3 months was equal to the average of the respective SDs across all other studies in the network to retain this study for inclusion in the NMA.

Table 9: Method of IOP assessment and data availability

Study	Outcome definition	Time point	Sufficient data
DuBiner *et al*. (2001)[16]	• Mean IOP	3 months • Baseline, Month 1, Month 3	Yes – sufficient data available.
Nixon *et al*. (2009)[10]	• Mean IOP • Absolute change from baseline	3 months • Baseline, Month 3	Yes – sufficient data available.

Rigollet *et al*. (2011)[8]	• Absolute decrease in IOP from baseline	12 months • Month 1, Month 2, Month 3, Month 4, Month 5, Month 6, Month 12	Yes – sufficient data available. Data management required to calculate SDs and IOP values at 3 months.
Katz *et al*. (2013)[12]	• Mean IOP (08:00, 10:00, 15:00, 17:00)	3 months • Baseline, Week 2, Week 6, Month 3	Yes – sufficient data available.
Whitson *et al*. (2013)[13]	• Mean IOP (08:00, 10:00, 15:00, 17:00) • Percentage reduction from baseline to 6 months • Absolute IOP change from baseline to 6 months	3 months with 3-month safety extension period • Week 2, Month 3	Yes – sufficient data available.
Kozobolis *et al*. (2017)[5]	• Mean morning and afternoon IOP (09:00, 16:00) • Mean IOP reduction from baseline	12 weeks • Week 1, Week 4, Week 8, Week 12	Yes – sufficient data available.
MERCURY 1[14]	• Mean IOP • Mean diurnal IOP • Percentage of patients achieving prespecified thresholds for mean diurnal IOP • Mean percentage change in mean diurnal IOP	12 months with 1 month extension period • Week 2, Week 6, Month 3, Month 9, Month 12, Month 13	Yes – sufficient data available.
MERCURY 2[15]	• Mean IOP • Mean percentage change in IOP • Percentage of patients achieving prespecified reduction in mean diurnal IOP	3 months • Week 2, Week 6, Month 3	Yes – sufficient data available.
MERCURY 3[6]	• Actual mean IOP (08:00, 10:00, 16:00) • Actual change from baseline (08:00, 10:00, 16:00) • Least squares change in actual IOP (08:00, 10:00, 16:00) • Mean diurnal (average hourly values: 08:00, 10:00, 16:00)	6 months (180 days) • Week 2, Week 6, week 12	Yes – sufficient data available.

Abbreviations: IOP – Intraocular pressure; NR – Not reported; SD – Standard deviation

Conclusion

It was determined that an NMA based on the connected network (Figure 5) consisting of nine RCTs to assess the percentage change in diurnal IOP from baseline was feasible.

NMA methodology

Indirect measures of treatment effect were estimated using both random effects and fixed effect models in accordance with the recommendations of the NICE DSU's Technical Support Documents (TSDs) on evidence synthesis, particularly TSD 2.[22]

The random effects model was the preferred analysis as it accounted for heterogeneity in treatment effects between studies. A fixed effect model assumes that in a network of evidence, all studies will show the same treatment effect. This assumption is underpinned by the assumption that the studies included in the network are suitably similar and entirely homogenous. On the other hand, a random effects model assumes that the treatment effect is not homogenous but varies between studies and treatment effects come from a common distribution. Fixed effect models are usually not realistic and lead to artificially narrow credible intervals.[23] The base case for this NMA considered the random effects model a priori. The fixed effect model was considered as a sensitivity analysis.

The choice of random effects in the base case was verified by considering the deviance information criterion (DIC). If the DIC was at least three points lower in the fixed effect model than the random effects model, that indicated that the fixed effect analysis appears to be a better fit to the data.[24]

Data management for NMA analyses

Before running the NMA analysis, the data was manipulated to derive diurnal IOP values and corresponding standard deviations (SDs) at each time point.

Diurnal IOP values were derived by averaging the IOP values at the different time points, at baseline and at the three-month follow-up. For example, to derive the diurnal IOP value for each treatment arm at baseline for Katz *et al*. (2013), an average of the IOP values at 8AM, 10AM, 3PM and 5PM at baseline was calculated.

Average SD of diurnal IOP was derived using the following formula:

$$Average\ SD = \sqrt{({s_1}^2 + {s_2}^2 + .. + {s_k}^2)/\ k}$$

Where s_k is the standard deviation for the k^{th} group and k is the total number of groups.

In the NMA analysis, the baseline and three-month diurnal IOP values and corresponding SDs were used to simulate the percentage change from baseline in diurnal IOP. 100,000 samples of the baseline and post-baseline (three-month) values were simulated using mvrnorm() in R based on the mean and variance reported. Correlation was assumed as 0.5. The 100,000 paired samples were used to calculate 100,000 percentage change from baseline estimates. Following this, the mean and standard deviation were calculated for the 100,000 estimates of percentage change from baseline.

Statistical model specification

A normal likelihood and identity link function were used to analyse the percentage change in diurnal IOP from baseline. Following NICE DSU TSD 2 guidance, for continuous outcome data, the meta-analysis is based on the sample means, y_{ik}, of arm k in trial i with a standard error of se_{ik}. Provided the sample sizes are not too small, the Central Limit Theorem allows us to assume that, even in cases where the underlying data are skewed, the sample means are approximately normally distributed, so that the likelihood can be written as:[22]

$$y_{ik} \sim N(\theta_{ik}, se_{ik}^2)\ (1)$$

The parameter of interest is the mean θik, of this continuous measure, which is unconstrained on the real line. The identity link is used, and the linear model can be written on the natural scale as:

$$\theta_{ik} = \mu_i + \delta_{i,bk} I_{\{k \neq 1\}}\ (2)$$

where μ is the study-specific baseline of study i, δ is the study-specific treatment effect in arm k relative to control treatment in arm b in study i, and I is defined as:

$$I_{\{u\}} = \begin{cases} 1 \; if \; u \; is \; true \\ 0 \; otherwise \end{cases} \quad (3)$$

Prior distributions

Non-informative conventional vague reference prior distributions were considered for mean treatment effects and trial-specific baseline treatment effects in the NMA:

- Mean of treatment effects, $d_{t_{i1}t_{ik}} \sim N(0, 100^2)$
- Trial specific baseline treatment effect, $\mu_i \sim N(0,100^2)$

An informative prior distribution was used to inform the between study standard deviation of treatment effects. The prior distribution selected was applied on the odds ratio (OR) scale and was obtained from Turner *et al.* (2015) for internal/external structure-related outcomes with a pharmacological versus pharmacological intervention.[25] To apply the prior on the difference scale for the analysis, the prior on the odds ratio scale was converted to the mean difference scale using the relationship reported by Ren *et al.* 2018[26]:

- Between study standard deviation, $\tau_{OR}^2 \sim LogNormal(-2.94, 1.79^2), \tau = \frac{\sqrt{3}\sigma\tau_{OR}}{\pi}$

The value of the standard deviation (1.51) was the average of the SDs from the percentage change from baseline data.

Model assessment

Convergence to the target posterior distributions was assessed using the Brooks-Gelman-Rubin (BGR) plots. A BGR plot was generated for each parameter that was monitored; if any of the parameters were matrices, each entry of the matrix was monitored. A BGR plot shows that the parameter has converged once the median shrink factor converges to 1 and 97.5% quartile of the shrink factor converges to some value (not necessarily 1). Prior distributions were tightened if there were problems with convergence. A suitable burn-in was selected and number of iterations of the Markov chain to estimate parameters was selected, allowing for thinning if required. The burn-in, number of iterations and thinning used for each outcome has been reported, aligning with NICE DSU guidelines.[27]

For each analysis, the goodness-of-fit to the model was assessed by using residual deviance and the DIC. When the residual deviance was close to the number of data points, it indicated that the model fit the data well. The DIC provided a relative measure of goodness-of-fit that penalised complexity and was used to compare alternative models.[28] A lower DIC value indicated that the model fit the data well. If the DIC for the fixed effect model was at least 3 points lower than for the random effects model, the fixed effect model was selected over random effects in the base case.

Software

OpenBUGS version 3.2.3 and R version 4.2.1 or above via RStudio was used to perform the analysis.[29,30] OpenBUGS was run from within R using the package 'R2OpenBUGS'.[31]

NMA results

Treatment effect of percentage change in diurnal IOP from baseline

Base case analysis (random effects model)

Results in Figure 6 show that, for the random effects analysis, patients treated with netarsudil-latanoprost had a greater percentage change in diurnal IOP from baseline compared to brinzolamide, brimonidine, latanoprost and travoprost-timolol (treatment effect [95% CrI]: [redacted] respectively). Considering the comparison of netarsudil-latanoprost with brinzolamide as an example, the results indicate that the reduction in diurnal IOP from baseline with patients who received netarsudil-latanoprost was 6.1 percentage points greater than for patients who received brinzolamide.

Furthermore, patients treated with netarsudil-latanoprost had a lower percentage change in diurnal IOP from baseline compared to brimonidine-timolol, dorzolamide-timolol, brinzolamide-brimonidine, latanoprost-timolol and bimatoprost-timolol (treatment effect [95% CrI]: [redacted], respectively). However, the

treatment effects for the comparison of netarsudil-latanoprost with all treatments are close to zero, indicating that these treatments have similar efficacy.

No results demonstrated statistical significance. However, the hypothesis of no difference is central in the credible intervals of all comparisons with netarsudil-latanoprost and so it can be concluded that there is no difference in treatment effect between the different treatment strategies.

Figure 6: Forest plot - percentage change in diurnal IOP from baseline (random effects model)

Abbreviations: IOP – Intraocular pressure; SD – Standard deviation
To achieve convergence, the burn-in was 100,000, with 50,000 iterations kept. The analysis was run with a thinning interval of 30.

Scenario analysis (fixed effect model)

Results in Figure 7 show that, for the fixed effect analysis, patients treated with netarsudil-latanoprost had a greater percentage change in diurnal IOP from baseline compared to brinzolamide, brimonidine, latanoprost and travoprost-timolol (treatment effect [95% CrI]:

respectively). Considering the comparison of netarsudil-latanoprost with brinzolamide as an example, the results indicate that the reduction in diurnal IOP from baseline with patients who received netarsudil-latanoprost was 6.1 percentage points greater than for patients who received brinzolamide.

Furthermore, patients treated with netarsudil-latanoprost had a lower percentage change in diurnal IOP from baseline compared to brimonidine-timolol, dorzolamide-timolol, brinzolamide-brimonidine, latanoprost-timolol and bimatoprost-timolol (treatment effect [95% CrI]: -

[redacted] respectively). However, the treatment effects for the comparison of netarsudil-latanoprost with all treatments are close to zero, indicating that these treatment arms have similar efficacy. No results demonstrated statistical significance. However, the hypothesis of no difference is central in the credible intervals of all comparisons and so it can be concluded that there is no difference in treatment effect between the different treatment strategies.

Figure 7: Forest plot - percentage change in diurnal IOP from baseline (fixed effect model)


[redacted]

Abbreviations: IOP – Intraocular pressure; SD – Standard deviation
To achieve convergence, the burn-in was 100,000, with 50,000 iterations kept. The analysis was run with a thinning interval of 30.

Treatment effect was comparable between the random effects and fixed effect models. As the residual deviance and DIC were within three points for both models (Table 10), the random effects model was retained for the base case. The between study SD was moderate, which suggests that the relative treatment effects, and thus results, are generally comparable across the studies considered.

Table 10: Key statistics for the random effects and fixed effect analyses of the treatment effect of percentage change in diurnal IOP from baseline

	Random effects	Fixed effect
Residual deviance	[redacted]	[redacted]
DIC	[redacted]	[redacted]
Between study SD	[redacted]	[redacted]

Abbreviations: DIC – Deviance information criterion; IOP – Intraocular pressure; SD – Standard deviation

NMA conclusion

The NMA analyses for percentage change in diurnal IOP from baseline show that netarsudil-latanoprost was more effective in increasing percentage change from

baseline in diurnal IOP compared to brinzolamide, brimonidine, latanoprost and travoprost-timolol. However, the results were not statistically significant for any of the treatment comparisons. The extremely small differences in treatment effect (<[redacted]) indicate negligible differences in treatment efficacy between all therapies considered in the NMA.

See the response to Question B5 for details of how the results of the NMA were applied in the cost-effectiveness model.

A9. PRIORITY. Document B, section B.2.9. Please explain the rationale for using percentage change in IOP, rather than mean IOP, as the outcome for the indirect treatment comparisons and for the economic modelling.

Using percentage change in IOP as the outcome for the ITC accounts for the range of initial baseline IOP levels from patients in the included trials. The ITC pools data from different trials where baseline characteristics and eligibility criteria were not identical, resulting in mean IOP being an inappropriate measure for a meaningful comparison of outcomes between the trials.

Prior to developing the economic model, UK clinical expert opinion was sought.[32] A model structure using a combination of IOP reduction and absolute IOP was proposed, using an absolute threshold of 24 mmHg, as defined in the NICE glaucoma guidelines (NG81) for OHT as the cut-off at which a clinician is recommended to offer a patient SLT or PGAs for initial treatment, or refer a patient for BB, CAIs, or sympathomimetic treatment for those who cannot tolerate their current treatment.[33] The clinician advised that use of an absolute threshold would not be suitable for modelling due to the variation in clinically acceptable/applicable target IOP ranges between patients, which is highly dependent on the severity of their condition.[32] OHT patients present with a wide range of IOP levels, whereas POAG patients often present with a much higher IOP level than OHT patients by definition.[32] For instance, patients with OAG may come in with a much higher IOP (as high as 40 mmHg in some cases), so the threshold of 24 mmHg would not be realistic to account for this population. Therefore, there are no standard thresholds which are applicable for all patients. Additionally, treatment choice for POAG and OHT patients is dependent on the level of IOP reduction from baseline that is required, so the use of percentage change in IOP as an outcome better reflects and aligns with the approach taken in UK clinical practice.[32]

By contrast, as explored in Question B2, the use of percentage change in IOP is supported by other published studies where IOP reduction thresholds of 20% and 30% were used as indicators of treatment success and set as a typical treatment target.[34–37] For reference, in the absence of UK-specific guidelines that apply for both POAG and OHT patients, the Canadian Ophthalmological Society's (COS) clinical practice guidelines recommends setting an upper limit of initial target IOP for each eye with a 20%, 25%, or 30% reduction in IOP from baseline, depending on the stage (decision to treat, early, and moderate/advanced, respectively) of the condition.[38] This aligns broadly with the thresholds used in our economic model (<20%, 20-30%, >30%).

Section B: Clarification on cost-effectiveness data

Literature searching

B1. PRIORITY. Document B, Section B.3.1, Published cost-effectiveness studies, page 99.

Please confirm why database searches for economic studies are limited to 2017-2022. Relevant articles that could provide valuable guidance on model structure and parameterisation might have been missed because of this restriction. Several examples of relevant cost-effectiveness models can be found in a recently published review of cost-effectiveness analyses for open-angle glaucoma management (https://journals.lww.com/glaucomajournal/Abstract/9900/A_Review_of_Cost_Effectiveness_Analyses_for.227.aspx). Please update the existing cost-effectiveness evidence summary, including a summary of relevant cost-effectiveness studies published before 2017.

As discussed in the response to Question A2, when conducting the initial SLR, a large number of hits (~10,000) were retrieved, prompting the use of a 5-year date cut-off and FDC comparator restriction. As agreed with the EAG during the clarification questions meeting (26th July 2023), targeted searches for evidence pre-2017 have now been conducted for clinical, cost-effectiveness, HRQoL, and cost and resource use studies. The search strategies are provided in Appendix A (Table 51, Table 52, Table 53, Abbreviations: HRQoL – health-related quality of life

Table *54*, Abbreviations: NHS – national health service; EED – economic evaluation database; HTA – health technology assessment; QoL – quality of life

Table *55*, Abbreviations: HRQoL – health-related quality of life; ScHARRHUD - School of Health and Related Research Health Utilities Database

Table *56*, Table 57) of this document.

The PRISMA diagram in Figure 1 (Question A2 response) summarises the screening of economic publications through each stage of the targeted database searches. The searches retrieved a total of 433 hits. After removing 24 duplicates, the titles and abstracts of 409 unique references were screened. 288 references were excluded

after the title and abstract screening. 121 unique references met the criteria for the full text review stage. Following the review of full texts, a total of 94 publications were excluded as they did not meet the selection criteria, leaving a total of 27 publications. Of this total, 18 publications met the selection criteria for the cost-effectiveness review question, and were data extracted.

In Appendix A of this document, please see a summary and a quality assessment of the cost-effectiveness studies extracted.

UK cost-effectiveness studies summary (n=5)

Hirst *et al.* 2013[39]

The identified publication was a cost utility analysis (CUA) assessing the cost-effectiveness of treatment with bimatoprost-timolol compared with dorzolamide-timolol and a non-fixed-dose combination of tafluprost-timolol for patients diagnosed with POAG. The cost-effectiveness was modelled from an NHS perspective with a lifetime horizon. Details of the model structure were not reported. Treatment with bimatoprost-timolol was associated with an incremental gain of 0.03 quality-adjusted life years (QALYs), dominating treatment with both dorzolamide-timolol and non-fixed-dose combination of tafluprost-timolol, and incurred a lower lifetime cost (£2,294 versus dorzolamide-timolol, and £2,919 versus non-fixed-dose combination of tafluprost-timolol). The probabilistic sensitivity analysis (PSA) showed that bimatoprost-timolol had a 98.8% probability of being cost-effective at a willingness to pay (WTP) threshold of £20,000/QALY.

From the results of the quality assessment, the risk of bias appears to be moderate.

Kobelt *et al.* 1999[40]

The publication was a cost-effectiveness analysis (CEA) aiming to estimate the impact of topical agents in glaucoma with products that control IOP for patients with newly diagnosed POAG or OHT that were initially treated with beta-blocker monotherapy. This was modelled from a societal perspective with a two-year time horizon. A Markov model structure was used, with seven health states defined according to the treatments patient received (first-line treatment, second line, combination therapy, trabecular surgery, laser surgery, post-surgery and first line post-laser surgery). Costs were based on the NHS in the UK and from observational studies in France, with the

cost year being 1997. The average cost per patient over 12 months for the standard therapy was £380 in the UK, with the average total costs of all the new treatments being lower than current therapy. The base case cost-effectiveness outcomes were not reported. Sensitivity analyses were performed for dorzolamide and latanoprost, where in the worst case with lowest effectiveness and no monotherapy, the costs were £332 for dorzolamide and £337 for latanoprost, respectively. In the best case, costs were £297 for dorzolamide and £301 for latanoprost, respectively. When the drug cost was varied, costs for dorzolamide ranged from £317 to £321, while costs for latanoprost ranged from £304 to £311.

From the results of the quality assessment, the risk of bias appears to be moderate.

Orme *et al.* 2012[41]

The publication was a CEA assessing the long-term economic consequences of managing glaucoma using latanoprost, bimatoprost, or travoprost as first-line treatment. The model used an NHS perspective with a 10-year time horizon, and a 3.5% discount rate was applied for both costs and outcomes. A Markov model structure was used, with the health states of OHT, mild glaucoma, moderate glaucoma, severe glaucoma, and death, and the following three triggers for a switch in medical therapy for glaucoma: lack of tolerance, IOP not meeting treatment benchmark, and glaucoma progression. Latanoprost as first-line treatment was associated with 5.87 QALYs, while both bimatoprost and travoprost were associated with 5.85 QALYs. The average cumulative costs per patient for treatment with latanoprost was £6,086.40 for latanoprost, £6,160.04 for bimatoprost, and £6,211.70 for travoprost. For the sensitivity analyses, using expert opinion data for treatment switches resulted in 5.87 QALYs and a total cost of £6,022.44 associated with latanoprost as first-line treatment, 5.86 QALYs and a total cost of £6,039.75 associated with bimatoprost as first-line treatment, as well as 5.86 QALYs and a total cost of £6,186.86 associated with travoprost as first-line treatment.

From the results of the quality assessment, the risk of bias appears to be moderate.

Holmstrom *et al.* 2006[42]

The publication evaluated the cost-effectiveness of bimatoprost, latanoprost, and timolol in France, Germany, Italy, Spain, and the UK in patients with POAG. The model

used a healthcare sector payer perspective over one year. A decision tree model was used to simulate the first year of glaucoma treatment with latanoprost, bimatoprost or timolol used in monotherapy. Patients initiated with a visit to the ophthalmologist and had two follow-up visits in the first three months followed by a full visit after one year once the patient reaches a stable IOP. If the IOP was not at the specified level after three months, adjunctive medication was added to the treatment, involving two extra follow-up visits to the ophthalmologist. The adjunctive medication was timolol if first-line therapy was bimatoprost or latanoprost. When timolol was first-line therapy the treatment added will be bimatoprost or latanoprost. If first-line therapy was bimatoprost and persistent adverse events occurred, the patient would change to latanoprost and vice versa. At an IOP of ≤13 mmHg, the incremental cost-effectiveness ratio (ICER) for bimatoprost was £18,541 while both timolol switching to latanoprost and latanoprost only dominated. This was similar at an IOP of ≤18mmHg, with the ICER for bimatoprost being £305. When effectiveness estimates were varied by ±10%, the treatments that were dominant and the dominated strategies did not change.

From the results of the quality assessment, the study appears to have a minimal risk of bias.

Wickstrøm *et al.* 2010[36]

A CEA was conducted to compare the cost-effectiveness of the fixed combinations of bimatoprost-timolol with latanoprost-timolol in Spain, Italy, Germany, the Netherlands, Norway, Sweden, Denmark, and the UK. The time horizon was three months. Bimatoprost-timolol was a dominating treatment strategy in all countries, with significantly more patients experiencing >15% and >20% reduction in IOP compared with latanoprost-timolol. Sensitivity analyses showed that results were largely insensitive to changes in key parameters.

From the results of the quality assessment, the study appears to have a high risk of bias.

Non-UK cost-effectiveness studies summary (n=13)

Bernard *et al.* 2003[43]

A CEA was conducted to assess the cost-effectiveness of treatment strategies with first line latanoprost compared with treatment using initial beta-blocker therapy in patients with OAG or OHT in France. The model used a third-party payer perspective with a two- and three-year time horizon. A 3% discount rate was assumed for costs and 0% for outcomes. A Monte Carlo simulation model was utilised with multistage treatment strategies where patients can either receive beta-blocker first line or latanoprost first-line treatment, switching to usual care second line or surgery if first-line treatment fails. All patients were assumed to undergo surgery upon failure of the sixth line treatment, with potential switching events every month. At a two-year period, latanoprost as first-line therapy had an incremental cost of €40.92 and 49.67 incremental days of IOP control, with an incremental cost of €0.82 per IOP-controlled day gained compared with beta-blocker. At a three-year period, latanoprost as first-line therapy had an incremental cost of €26.59 and 73.74 incremental days of IOP control, with an incremental cost of €0.36 per IOP-controlled day gained compared with beta-blocker. The analysis was sensitive to time to therapy failure, bottle duration, assessment visit schedule for patients who switched treatments, surgical rates, and cost of surgical procedures.

From the results of the quality assessment, the risk of bias of the study appears to be minimal.

Blaser *et al.* 2011[44]

The publication used a CEA to evaluate the most cost-effective formulary management strategy of ophthalmic prostaglandins from the perspective of a managed care organisation for patients with OAG or OHT. This was modelled over a one year time horizon in the United States (US). The resulting ICER for first-line treatment with bimatoprost was $815.13, $961.71 for latanoprost, and $889.13 for travoprost per effectively treated patient. The ICER for first-line treatment with timolol followed by a preferred prostaglandin was $436.77 for bimatoprost, $499.77 for latanoprost, and $462.21 for travoprost per effectively treated patient. If a preferred prostaglandin was not selected, the ICERs were $910.95 for first-line therapy and $477.77 for second line therapy per effectively treated patient. Sensitivity analyses showed that reducing the price of latanoprost by 9% and travoprost by 3% yielded equivalent ICERs as bimatoprost.

Based on the results of the quality assessment, the study appears to have a high risk of bias.

Cottle *et al.* 1988[45]

A CEA was conducted to examine the cost-effectiveness of parasympathomimetics prescribed during the first year of treatment in patients with newly diagnosed and untreated POAG in Canada. This was modelled over a one year time horizon. The outcomes were presented as the monthly cost per usefulness quotient, which was the number of patients whose condition was controlled with mild or no adverse reactions divided by the number of patients who started on the treatment. The cost-effectiveness ratios were 2.08 for pilocarpine 2% QID, 3.08 for pilocarpine 1% QID, 8.89 for timolol 0.25% QID, 8.28 for timolol 0.5% BID, and 4.08 for dipivifrin 0.1% QID.

From the results of the quality assessment, the risk of bias appears to be high.

Kymes *et al.* 2006[46]

The publication carried out a CUA to determine which patients would benefit from treatment in patients with IOP ≥24 mmHg. This was modelled from a societal perspective over a lifetime horizon with a 3% discount rate for costs and benefits in the US. A Markov model was utilised where all patients had OHT and could remain, die, or progress to the next health state from where they started in during a year. The ICER for treating patients with a ≥5% annual risk of developing POAG versus treating no one was $3,670/QALY. The ICER for treating patients with a ≥5% annual risk of developing POAG versus treating patients with a ≥2% annual risk of developing POAG was $42,430/QALY. Treating all patients was dominated by treating patients with a ≥2% annual risk of developing POAG. Assuming a cost-effectiveness threshold of $50,000 to 100,000/QALY, the treat ≥2% threshold resulted in the most net health benefit. The decision was sensitive to the incidence of POAG without treatment, treatment effectiveness, and the utility loss because of POAG.

From the results of the quality assessment, the risk of bias appears to be moderate.

Kymes *et al.* 2010[47]

A CUA in the US aimed to evaluate the influence of age and/or expected lifespan in determining the cost-effectiveness of treating OHT with standard of care to prevent POAG. This was modelled from a societal perspective for a lifetime horizon with a 3%

discount for costs and outcomes, and with patients at a baseline age of 45, 55, and 65. A Markov decision model described the progression to the first or second stage of glaucoma iteratively until the cohort died of other causes. To be cost-effective when the WTP threshold was $50,000 and with 2% of patients treated, those aged 45 needed a life expectancy of 21 years, those aged 55 needed 24 years, and patients aged 65 needed 26 years. To be cost-effective when the WTP threshold was $100,000 and with 5% of patients treated, those aged 45 needed a life expectancy of 7 years, those aged 55 needed 8 years, while those aged 65 needed 17 years. From sensitivity analyses, the utility loss associated with progression to the first stage of POAG was an important factor for determining cost-effectiveness.

From the results of the quality assessment, the risk of bias appears to be moderate.

Marchetti *et al.* 2001[48]

The study conducted a CEA to compare the cost-effectiveness of brimonidine 0.2% and betaxolol 0.25% as first line treatments for patients with newly diagnosed or currently untreated OHT or OAG in the US. A decision tree model was used with the outcomes being clinical success or failure and was modelled over a one year time horizon. The cost-effectiveness ratio of expected costs against clinical success rate was $407.81 for brimonidine, and $583.97 for betaxolol. After sensitivity analyses, the results were considered robust and stable. For brimonidine to lose its higher ranking to betaxolol, its drug acquisition price would have to increase from $20.17 to $60.26, or the price of betaxolol would have to diminish from $20.79 to $6.40.

From the results of the quality assessment, the risk of bias appears to be high.

Peeters *et al.* 2012[37]

A CEA aimed to determine the effectiveness of OHT treatment initiated with latanoprost compared with timolol in The Netherlands. This was modelled from a healthcare perspective over a lifetime horizon in patients with POAG, with a 4% discount rate for costs and effects. A decision tree model was used to model therapy adjustments while lifelong follow-up and disease progression was modelled in a Markov model. The health states during follow-up were death, glaucoma, and blindness. The ICER of starting with latanoprost versus starting with timolol was €535,852 when initial IOP was sampled from distribution, €547,276 when initial IOP

was 25 mmHg, and €7,068,037 when initial IOP was 30 mmHg. Variation of contraindication for timolol and side-effects of medication within the given ranges did not greatly influence outcomes.

From the results of the quality assessment, the risk of bias of the study appears to be minimal.

Rocchi *et al.* 1997[49]

The publication conducted a CUA to compare dorzolamide to pilocarpine as adjunctive treatments in patients with POAG over 65 years of age in Canada. A simplified clinical process was used where patients failed therapy when they discontinued due to intolerable adverse events or succeeded when therapy was maintained. This was modelled from a provincial ministry of health perspective for a 10 year time horizon with a 5% discount for costs and consequences. The ICER for dorzolamide versus pilocarpines was $9,490/QALY. When the adverse event rates were changed, the resulting cost-effectiveness ratio was still favourable for dorzolamide even when the adverse event rate for pilocarpine was halved.

From the results of the quality assessment, the risk of bias appears to be minimal.

Rouland *et al.* 2003[50]

The study compared the direct medical costs of topical brinzolamide 1% with dorzolamide 2% in France, Italy, Portugal, and Spain using a cost-minimisation analysis (CMA) in patients with POAG or OHT who had not responded to or could not tolerate beta-blocker therapy. This was from a payer perspective with a time horizon of three months. A decision tree model considered whether brinzolamide or dorzolamide were used as a monotherapy or concomitantly with a beta-blocker, and allowed for treatment switching in case of intolerance or lack of efficacy. The baseline breakeven price for France was €14.72, €15.43 for Italy, €15.81 for Portugal, and €15.21 for Spain. The average savings per patient was -€0.03 in France, €1.17 in Italy, €2.03 in Portugal, and €3.05 in Spain.

From the results of the quality assessment, the risk of bias appears to be moderate.

Stein *et al.* 2012[51]

A CUA aimed to determine the most cost-effective treatment option between topical prostaglandins or laser trabeculoplasty for patients aged 60 years with mild OAG in the US. A Markov model with the health states of mild glaucoma, moderate glaucoma and severe glaucoma, unilateral blindness, bilateral blindness, and death were used. A 3% discount for costs was applied and a time horizon of 25 years was used. The base case ICER was $16,824/QALY for laser trabeculoplasty versus no treatment, and $14,179/QALY for prostaglandins versus no treatment. In a two-way sensitivity analysis varying the effectiveness of prostaglandins and laser trabeculoplasty, laser trabeculoplasty was the preferred treatment option when the effectiveness of prostaglandins was 25% lower. Similarly, if the effectiveness of laser trabeculoplasty was 20% or greater less effective, laser trabeculoplasty was the preferred option.

From the results of the quality assessment, the risk of bias appears to be minimal.

Stewart *et al.* 2008[52]

The publication assessed the long-term cost-effectiveness of OHT treatment represented by an average of latanoprost, bimatoprost, travoprost, generic timolol, and brimonidine for patients with OHT in the US using a CUA. A Markov model was used with the health states of stable OHT and glaucoma over a five-year time horizon with a discount rate of 3% for costs. The baseline ICER was $89,072 which was the cost of preventing one patient from progressing to POAG if all OHT patients received treatment. The risk factor analyses ICERs for an additional one decade of age was $62,756, an additional 5mmHg of IOP was $40,157, an additional cup-to-disc ratio of 0.5 was associated with an ICER of $55,431, and an additional corneal thickness of 40µm was $36,683. A ±10% change of price in argon laser trabeculoplasty, cost of medication, or cost of a non-comprehensive follow-up visit altered the ICER by $10,000 or less.

From the results of the quality assessment, the risk of bias appears to be moderate.

van Gestel *et al.* 2014[53]

A CUA was conducted to assess the long-term cost-effectiveness of initiating treatment for OHT for patients with an initial IOP of 25mmHg in The Netherlands. A patient-level simulation model captured a patient's first ophthalmologist visit, and subsequent advancement including conversion from OHT to POAG and death. This

was modelled from a societal perspective over a 10 year or lifetime horizon, with a 4% discount for costs and 1.5% discount for outcomes. The discounted ICER of direct treatment versus watchful waiting was €33,645 for a 10-year time horizon, and was dominant for a lifetime horizon. At a WTP threshold of €0/QALY, the probability that direct treatment is cost-effective was 83%. At thresholds of €10,000/QALY and higher, this probability had increased to 100%.

From the results of the quality assessment, the risk of bias appears to be minimal.

van Gestel *et al.* 2012[54]

The study compared the long-term cost-effectiveness of four treatment strategies involving latanoprost, a target IOP of 15mmHg, visual field measurements every 6 months, or visual field measurements every 24 months, in patients with POAG in the Netherlands using a CUA. A discrete event simulation model was used with a lifetime horizon and societal perspective. This was modelled with a 4% discount rate on costs and 1.5% discount rate on effects. The ICER for latanoprost was €12,931/QALY gained, and €173,486/QALY for visual field measurements every six months, and €21,516/QALY for visual field measurements every 24 months. The treatment strategy of targeting IOP was dominant.

From the results of the quality assessment, the risk of bias appears to be minimal.

The Sood *et al*. 2023 paper detailed in the question includes 16 papers of interest.[55] Table 11 demonstrates which of these papers were captured by the targeted searches and reasons for exclusion. Most of the papers were retrieved by the updated targeted searches but were excluded on the basis of population (most did not include a strictly POAG and/or OHT population). Three of the papers (pre-2017) were extracted as part of the updated targeted searches, and four papers were excluded from the original SLR (2017-2022).

Table 11: Publications from Sood et al. 2023

Paper	Reason for exclusion/retrieved by searches?
Pre-2017: In the scope of additional pre-2017 targeted searches (n=12)	
Marchetti et al. 2001	Extracted as part of updated economic TLR.
Walt et al. 2004	Excluded for population: Glaucoma/OHT - doesn't specify which glaucoma types.

Goldberg et al. 2006	Excluded for population: Glaucoma patients (subtype not specified)
Fiscella et al. 2006	Excluded for population: Not POAG and/or OHT
Noecker et al. 2006	Excluded for population: Glaucoma/OHT - doesn't specify which glaucoma types.
Frenkel et al. 2007	Not captured in Economic TLR: Monotherapies only.
Rein et al. 2009	Excluded for population: Not POAG and/or OHT
Kymes et al. 2010	Extracted as part of updated economic TLR.
Stein et al. 2012	Extracted as part of updated economic TLR.
Li et al. 2013	Excluded for population: Not POAG and/or OHT, normal tension glaucoma
Kaplan et al. 2015	Not captured in Economic TLR: No direct comparator included.
Pizzi et al. 2016	Not captured in Economic TLR: No direct comparator included.
Post-2017: In the scope of the original SLR post-2017 (Table 8 of Appendix D.2.4 of submission) (n=4)	
Brown et al. 2019	Excluded for population: Not a western country
Newman-Casey et al. 2020	Excluded for population: No separate data on POAG patients. Reported as glaucoma
Elhusseiny et al. 2021	Excluded for population: No data on type of glaucoma
Sood et al. 2021	Excluded for population: No data on type of glaucoma, only reported on stages

Abbreviations: OHT – Ocular hypertension; POAG – Primary open-angle glaucoma; SLR – Systematic literature review; TLR – Targeted literature review

Economic modelling (structure)

B2. PRIORITY. Document B, Section B.3.2.2, Model structure, pages 102-106.

We consider the current model health states to be inadequate to capture the full impact of changes in IOP on glaucoma disease progression. Please rebuild the economic model, using health states that capture the impact of absolute mean IOP on disease progression. Such a model could utilise a linked evidence approach, linking IOP (rather than changes in IOP from baseline) to glaucoma disease progression. Health states could include, for example, mild, moderate and severe disease, and could potentially consider additional states to capture unilateral or bilateral blindness. Please see Stein et al., 2012 (https://jamanetwork.com/journals/jamaophthalmology/fullarticle/1150923) for one possible example of a more appropriate model structure:

As described in Question B1, and as agreed with the EAG during the clarification questions meeting (26th July 2023), targeted searches for economic evidence pre-

2017 have been conducted, in addition to a SLR which was conducted between 2017 to the present time as part of the NICE submission. Additional targeted searches were also conducted for this question to identify any publications which define a mapping between IOP and glaucoma disease progression.

Multiple studies were identified from the economic searches which used absolute mean or percentage change in IOP as an outcome. However, the IOP thresholds defined across the studies varied and there was no clear consensus in linking these thresholds to glaucoma disease progression or severity health states. **Error! R eference source not found.**Furthermore, no OHT or POAG guidelines have directly specified an accepted absolute or percentage reduction IOP threshold linked to glaucoma disease progression. As described in the response to Question A9, this is primarily due to the fact that there is large variation in clinically acceptable/applicable target IOP ranges between patients in clinical practice, which is highly dependent on the severity of their condition at baseline. OHT patients present with a wide range of IOP levels, whereas POAG patients often present with a much higher IOP level than OHT patients by definition.[32] This was confirmed by UK clinical experts whilst developing the model, and is also supported by published statements which suggest that target IOP levels are not static but change constantly.[34,56] Therefore, it is not appropriate to consider glaucoma progression health states in terms of absolute IOP, since there is wide variation in the definitions of glaucoma severity based on IOP as shown in Table 12. Hence, it is more appropriate to consider percentage changes in IOP as an outcome to assess how well a treatment works in reducing this variable throughout its use (and subsequently glaucoma disease progression), as it is not defined by a fixed absolute IOP level or state. In UK clinical practice, treatment choice for POAG and OHT patients is dependent on the level of IOP reduction from baseline that is required, so the use of percentage change in IOP as an outcome better reflects and aligns with this approach.[32]

Considering this and as stated in the response to Question A9, health state definition selection was based on thorough UK clinical expert validation, details from published studies and guidelines (NICE, Canadian Ophthalmological Society and European Glaucoma Society) to account for varying patient targets, baseline IOP levels, and

clinical trial sources. In line with this reasoning, we consider the current health states and model structure to be appropriate.

While not applying the study's structure directly as health states, Stein *et al*. (2012)[51] is indirectly incorporated into the model in the form of the quality-of-life values for each of the health states. As detailed in Question B12, a scenario has been added to the model and submission to reflect the use of the quality-of-life values used in Stein *et al*. (2012)[51], assuming an analogous relationship between mild, moderate and severe in the publication, and the >30%, 20-30%, and <20% reduction in IOP health states in the model. An equivalent assumption and mapping are applied for the Orme *et al*. (2012)[41] data.

Table 12: IOP thresholds used in published literature

Study	IOP thresholds/health states used
Broadly support the model approach	
Gazzard 2019[57], based on Damji and Behki (2003)[58]	Target for OAG: • Mild: <21 mmHg or >20% reduction • Moderate: <18 mmHg or >30% reduction • Severe: <15 mmHg, >30% reduction Target for OHT: • Mild: <25 mmHg, >20% reduction
Peeters 2012[37]	Health states: • ≤21 mmHg • >21 mmHg and >20% reduction. • >21 mmHg and <20% reduction.
Wickstrom 2010[36]	Health states: • >15% reduction in IOP • >20% reduction in IOP
Orme 2010[59]	IOP ≥20% reduction (at initial visit), and IOP<20 mmHg (at subsequent visits)
Stewart 2008[52] (using European glaucoma society thresholds)	Stops progression from OHT to POAG • IOP ≤24 mmHg, >20% reduction
Rouland 2005[35]	IOP target range: • 8-21 mmHg, usually requiring 30% reduction
Griffin 2019[34]	Target IOP: • Mild: 18 mm Hg • Moderate: 15 mm Hg • Severe: 12 mm Hg • Reasonable initial treatment: 30% below baseline
Lin 2014[60]	Treatment success: • ≥30% reduction in IOP

Study	IOP thresholds/health states used
Glaucoma today guidelines (CIGT guidelines)[56]	Target IOP: • Early: <21mm Hg + >25% reduction (or >30% in CITGS) • Moderate: >18mmHg + 30-35% reduction • Severe: >18mmHg + average 10-12mmHg + near episcleral venous
Does not support the approach in the model	
Sihota 2018[61]	• Mild: 15-17 mmHg • Moderate: 12-15 mmHg • Severe: 10-12 mmHg
NICE guidelines NG81 2017[33]	Required for PGA and other treatment eligibility: ≥24 mmHg
Van Gestel 2014[53]	Intervention: • OHT target: 21mmHg • POAG target (1st progression): 18mmHg • Progression (2nd progression): 15mmHg
Van Gestel 2012[54]	• Target: 21mmHg • POAG targe (1st progression): 18mmHg • Progression (2nd progression): 15mmHg
Craven 2012[62]	• Mild: >22 mmHg (implied) • Mild to moderate: 22-36 mmHg • Severe: >36 mmHg (implied)
Musch 2012	Analysis proportions: • <22 mm Hg • <20 mm Hg • <18 mm Hg • <16 mm Hg
Katz 2012[63]	Eligibility requirements: • Higher eye: IOP ≥24 and <34 mmHg • Lower eye: IOP ≥20
Blaser 2011[44]	Effectively treated after three months: • IOP < 18 mmHg
Lai 2004[64]	Failed treatment: • >21 mmHg
AGIS investigators 2000[65]	Health states: • >17.5 mm Hg • 14-17.5 mm Hg • <14 mm HG
Chen 2000[66]	• Normal: 21 mmHg • Early: 17-19 mmHg (upper teens) • Moderate: 14-16 mmHg (mid-teens) • Advanced: 11-13 mmHg (low teens)

Abbreviations: CITGS – Collaborative Initial Glaucoma Treatment Study; IOP – Intraocular pressure; mmHg – Millimetres of mercury; OHT – Ocular hypertension; PGA – Prostaglandin analogue; POAG – Primary open-angle glaucoma

Economic modelling formulae

B3. Economic model file.

An initial review of the submitted economic model has identified some minor modelling and formula errors. Please check the following:

A) The labelling and alignment of cumulative persistence parameters applied in the model (see Tab "clinical inputs", cells: "BK960: DE960"). Please add clearer labels to ensure that the formulae can be checked for accuracy. Please confirm that the formulae are implemented as described in the submission document (Table 47, page 115).

B) There appears to be a minor discrepancy between the model calculation (tab: "Data store", cell "H468") and the reported value for A&E resource use frequency for the >30% reduction in IOP state in the company submission (See document B, Table 57, p.125). Please check and confirm the correct value.

C) Please check if the £0 treatment acquisition cost per cycle entered in the tab: "Data store", cell: "I400" is correct.

A) The model has been updated to include these changes. Tables in 'Clinical inputs CH960-HH1817' have been moved to 'Clinical inputs BE967-DE1821'.

The company confirms that the formulae are applied as described in the submission document (Table 47, page 115).

B) There is a typographical error in Document B of the company submission; the model value is correct at 0.011. Rows 4-6 in Table 57 of Document B should read as follows (changes highlighted bold):

Table 13: Corrected data for Document B, Table 57, rows 4-6

A&E attendance	143.74	NHS: Total outpatient attendance #180 Emergency Medicine Service	<20% reduction in IOP	**0.011**	1.65
			20% - 30% reduction in IOP	0.011	1.61
			>30% reduction in IOP	**0.011**	1.57

Abbreviations: A&E – Accident and emergency; IOP – Intraocular pressure; NHS – National Health Service

C) There is a typographical error in the economic model, which has now been corrected: 'Data store' cell H425 has been edited to include the formula "=H1013", resulting in cell I419 to equal £6.33.

The change is negligible, since the market share of the product with error is only 0.06% of the Latanoprost & Timolol basket. Subsequently, cell L419 does not change at two decimal places (£11.37), with £11.3676 becoming £11.3704. Consequently, further results and reporting in the submission remain unchanged.

Transition probabilities

B4. PRIORITY. Section B.3.3.2 Transition probabilities, page 108.

Please provide further details regarding the "patient-level data analysis from the MERCURY 3 trial" that was used to inform the transition probabilities in the economic model for netarsudil-latanoprost and bimatoprost-timolol. Please provide the following information:

A) Were transition probabilities based on the intention-to-treat dataset?

B) Were transition probabilities based on complete data at each time point, complete data across all time points, or based on any imputation of missing data? If data imputation was used, please provide details of imputation methods.

C) Were transition probabilities based on the best, worst, or average of IOP in both eyes? Please provide details of transition probabilities derived from all three categories and comment on which approach is most appropriate for decision modelling.

D) Please provide the number of patient data points available for the calculation of each cycle-specific transition probability from the MERCURY 3 study.

E) Please comment on any implications of missing data for transition probability calculation.

The below responses relate to the calculation of the study eye transitions, as included in the original submission. The fellow eye calculations applied an equivalent methodology.

A) Yes, the transition probabilities were based on IOP individual patient level data (IPD) that consists of the intention-to-treat (ITT) population (430 subjects). Nine patients were removed from this dataset (transition probability data in the model includes 421 subjects) due to missing data, i.e., patients who had no post-baseline (visit 3) diurnal IOP values were removed entirely. See Section B.3.3.2 of the original submission for details of the transition probabilities methodology.

B) If patients had no post-baseline (V3) diurnal IOP values in the IPD data, they were removed from the total transition population pre-analysis. If patients were missing diurnal IOP values for some visits, they were not counted in the total population for that visit. When later values were available, transitions were calculated only if data for two consecutive visits were available. This avoids any assumptions around patients remaining in the same health state when data were missing and ensuring all transitions consider only a month-long period. If patients had <3 readings for a visit (missing data at 08:00,10:00, or 16:00), meaning the diurnal value was not provided, that visit was considered missing to ensure consistency of diurnal measurement i.e., all diurnal values were averages of three readings (08:00, 10:00, and 16:00).

C) As described in further detail below in the response to Question B13, most analyses published from MERCURY 3 were based on the 'study eye', which was the patient's 'worst-seeing' eye. The base case analysis in the model is based on the study ('worst-seeing') eye, but a sensitivity analysis has since been included in the model using 'fellow eye' data for the transition matrices (further detail provided in response to Question B18). Due to the minimal insights available, with an artificial reduction of IOP and misrepresented severity of disease, an average approach has not been included. A comparison of the data for the two eyes is provided in response to Question B13.

   As detailed in the Question B13 response, most comparator studies included only patient's 'worst-seeing' eyes. Given that baseline IOP is influential on

patient IOP reduction (as stated in clinical expert advice[32], see question A9), and that in clinical practice, patients receive targets based on IOP level, sometimes different for each eye[38], using the 'fellow eye' data from MERCURY 3 in the base case would make for an unfair comparison. In conclusion, 'study eye' data is the most appropriate for decision modelling.

D) Table 14 provides the number of patient data points available for each treatment arm from the MERCURY 3 trial, and the total transition population for each visit/cycle post-calculation. The discrepancy between the 'data points available' and 'transition count total population' is driven by the requirement for patients to have two consecutive visit readings to be included in the transition calculation (see response to Question B4. B). This was used to ensure consistency (all transitions consider only a month-long period) and avoid assumptions around patients remaining in the same health state when data were missing.

Table 14: Transition probability data points and counts

	Netarsudil-latanoprost		Bimatoprost-timolol	
	Data points available	**Transition count total population**	**Data points available**	**Transition count total population**
Visit 3	[redacted]	Baseline: NA	[redacted]	Baseline: NA
Visit 4	[redacted]	Month 1: [redacted]	[redacted]	Month 1: [redacted]
Visit 5	[redacted]	Month 2: [redacted]	[redacted]	Month 2: [redacted]
Visit 6	[redacted]	Month 3: [redacted]	[redacted]	Month 3: [redacted]

Abbreviations: NA - not applicable

E) Patients who had consistent missing data post-baseline were removed from all analyses, meaning the total analysis population is shrunk, thereby reducing statistical power.

Missing data for some visits reduced the analysis population for that visit (and the following visit), reducing statistical power for those visits. The reasons for missing data per visit are not provided within the CSR, reducing the inferences that can be made. However, reasons for study discontinuation were provided, presented in Table 39 (in response to question B13, below), indicating that subject discontinuation was mostly from AEs in the netarsudil-latanoprost arm,

with minimal rates elsewhere and similar rates of loss to follow-up across the netarsudil-latanoprost and bimatoprost-timolol arm. Given that much of this missing data pertains to patients who missed individual visits but returned for later visits, not discontinuing from the trial completely, a temporary lack of patient availability is the expected reasons for this missing data, suggesting no considerable bias is incurred.

Likewise, those patients who missed some readings within visits (compromising of the diurnal measurement) were removed from that visit, reducing the analysis population for that visit (and the following visit). The equivalent reasoning applies to statistical power and expected bias from missed visits. In conclusion, it is hypothesized that missing data only reduces the population size and statistical power, which do not bias the data in any direction.

Though the IPD data used for the transition probabilities in the model used raw (observed) data without imputation (N=[redacted]), for the primary endpoint analysis in the trial, imputation was performed (N=[redacted]). Using multiple techniques and assuming missing at random, scenarios were presented for both with and without multiple imputation (observed, last observation carried forward, baseline observation carried forward). Results were consistent across both scenarios, indicating that missing data are not influential on the analysis, and demonstrating that the transition probabilities are reflective of the primary presented analysis in the CSR.

B5. PRIORITY. Section B.3.3.2 Transition probabilities, pages 108-111.

Comparator effectiveness for the economic model is obtained from an STC and MAIC for the following treatments: dorzolamide-timolol, brimonidine-timolol and brinzolamide-brimonidine. The company submission, page 109 states that "…*an STC and MAIC were conducted to inform comparative efficacy inputs, given the absence of clinical trials directly comparing netarsudil-latanoprost and other FDC comparators*". Efficacy parameters for the remaining comparators were "*assumed to be equivalent to a drug from the ITC within the same treatment class*" (page 111).

Given the concerns raised in clarification queries in Section A above, we are not satisfied that a lack of sufficient clinical effectiveness data from trials to populate the

model has been adequately demonstrated. Please complete a full clinical effectiveness SLR, addressing concerns raised in Section A, and where possible, please update the comparator effectiveness estimates used in the model based on a network-meta-analysis that incorporates all the available evidence.

Response

As agreed during the clarification question call with the EAG on 26th July 2023, targeted database searches have been performed to identify additional relevant clinical effectiveness studies that could be included in an NMA. Please refer to the response to Question A8 for details of the searches undertaken, the clinical studies identified and details of the NMA (feasibility assessment, methodology and results) that was subsequently undertaken.

Table 15 summarises the sources used for comparator class efficacy data. As detailed in Appendix J of the original submission, the PLD from MERCURY 3 was directly used to inform the transitions between the health state in the model for netarsudil-latanoprost and bimatoprost-timolol. In response to the EAG, comparative efficacy has been derived for the following FDC comparators via an NMA: latanoprost-timolol, travoprost-timolol, brinzolamide-brimonidine, dorzolamide-timolol and brimonidine-timolol.

Two of the FDC comparators in the model, brinzolamide-timolol and tafluprost-timolol, were not included in MERCURY 3 or the NMA. Therefore, their efficacy was assumed to be equivalent to the comparator of the corresponding drug class; for brinzolamide-timolol, efficacy data was assumed equal to dorzolamide-timolol, and for tafluprost-timolol, efficacy data was assumed equal to bimatoprost-timolol.

Table 15: Comparator class efficacy data source

Comparator class	Comparator	Source of efficacy data
RKI + PGA	Netarsudil-latanoprost	MERCURY 3[6]
CAI + BB	Dorzolamide-timolol	NMA
	Brinzolamide-timolol	Assumed equal to dorzolamide-timolol
CAI + SYMP	Brinzolamide-brimonidine	NMA
SYMP + BB	Brimonidine-timolol	NMA
PGA + BB	Bimatoprost-timolol	MERCURY 3[6]
	Latanoprost-timolol	NMA

	Tafluprost-timolol	Assumed equal to bimatoprost-timolol
	Travoprost-timolol	NMA

Abbreviations: BB – Beta-blocker; CAI – Carbonic anhydrase inhibitor; NMA – Netwrok meta-analysis; PGA – Prostaglandin analogue; RKI – Rho Kinase Inhibitor; SYMP – Sympathomimetic

Transition probabilities for each intervention are presented in Table 16 to Table 24. Figure 8 to Figure 16 display the proportion of patients in each health state over the model time horizon for each comparator. Please note that no changes have been made to the transition probabilities for netarsudil-latanoprost and bimatoprost-timolol as they were derived from PLD.

Transition probabilities: netarsudil-latanoprost

Table 16: Netarsudil-latanoprost transition probabilities (informed by MERCURY 3)

Cycle	Health state	<20% reduction in IOP	20% - 30% reduction in IOP	>30% reduction in IOP
Baseline -> Cycle 1	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 1 -> Cycle 2	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 2 -> Cycle 3	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – Intraocular pressure

Figure 8: Netarsudil-latanoprost results - proportion of patients in each health state over the model time horizon

Abbreviations: IOP – Intraocular pressure

Transition probabilities: dorzolamide-timolol

Table 17: Dorzolamide-timolol transition probabilities (derived using NMA output)

Cycle	Health state	<20% reduction in IOP	20% - 30% reduction in IOP	>30% reduction in IOP
Baseline -> Cycle 1	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 1 -> Cycle 2	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 2 -> Cycle 3	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – Intraocular pressure; NMA – Network meta-analysis

Figure 9: Dorzolamide-timolol results - proportion of patients in each health state over the model time horizon

Abbreviations: IOP – Intraocular pressure

Transition probabilities: brinzolamide-timolol

Table 18: Brinzolamide-timolol transition probabilities (assumed equal to dorzolamide-timolol)

Cycle	Health state	<20% reduction in IOP	20% - 30% reduction in IOP	>30% reduction in IOP
Baseline -> Cycle 1	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 1 -> Cycle 2	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 2 -> Cycle 3	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – Intraocular pressure

Figure 10: Brinzolamide-timolol results - proportion of patients in each health state over the model time horizon

Abbreviations: IOP – Intraocular pressure

Transition probabilities: brinzolamide-brimonidine

Table 19: Brinzolamide-brimonidine transition probabilities (derived using NMA output)

Cycle	Health state	<20% reduction in IOP	20% - 30% reduction in IOP	>30% reduction in IOP
Baseline -> Cycle 1	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 1 -> Cycle 2	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 2 -> Cycle 3	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – Intraocular pressure; NMA – Network meta-analysis

Figure 11: Brinzolamide-brimonidine results - proportion of patients in each health state over the model time horizon

Abbreviations: IOP – Intraocular pressure

Transition probabilities: brimonidine-timolol

Table 20: Brimonidine-timolol transition probabilities (derived using NMA output)

Cycle	Health state	<20% reduction in IOP	20% - 30% reduction in IOP	>30% reduction in IOP
Baseline -> Cycle 1	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 1 -> Cycle 2	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 2 -> Cycle 3	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – Intraocular pressure; NMA – Network meta-analysis

Figure 12: Brimonidine-timolol results - proportion of patients in each health state over the model time horizon

Abbreviations: IOP – Intraocular pressure

Transition probabilities: bimatoprost-timolol

Table 21: Bimatoprost-timolol transition probabilities (informed by MERCURY 3)

Cycle	Health state	<20% reduction in IOP	20% - 30% reduction in IOP	>30% reduction in IOP
Baseline -> Cycle 1	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 1 -> Cycle 2	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 2 -> Cycle 3	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – Intraocular pressure

Figure 13: Bimatoprost-timolol results - proportion of patients in each health state over the model time horizon

Abbreviations: IOP – Intraocular pressure

Transition probabilities: latanoprost-timolol

Table 22: Latanoprost-timolol transition probabilities (derived using NMA output)

Cycle	Health state	<20% reduction in IOP	20% - 30% reduction in IOP	>30% reduction in IOP
Baseline -> Cycle 1	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 1 -> Cycle 2	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 2 -> Cycle 3	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – Intraocular pressure; NMA – Network meta-analysis

Figure 14: Latanoprost-timolol results - proportion of patients in each health state over the model time horizon

Abbreviations: IOP – Intraocular pressure

Transition probabilities: tafluprost-timolol

Table 23: Tafluprost-timolol transition probabilities (assumed equal to bimatoprost-timolol)

Cycle	Health state	<20% reduction in IOP	20% - 30% reduction in IOP	>30% reduction in IOP
Baseline -> Cycle 1	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 1 -> Cycle 2	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 2 -> Cycle 3	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – Intraocular pressure

Figure 15: Tafluprost-timolol results - proportion of patients in each health state over the model time horizon

Abbreviations: IOP – Intraocular pressure

Transition probabilities: travoprost-timolol

Table 24: Travoprost-timolol transition probabilities (derived using NMA output)

Cycle	Health state	<20% reduction in IOP	20% - 30% reduction in IOP	>30% reduction in IOP
Baseline -> Cycle 1	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 1 -> Cycle 2	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]
Cycle 2 -> Cycle 3	<20% reduction in IOP	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – Intraocular pressure; NMA – Network meta-analysis

Figure 16: Travoprost-timolol results - proportion of patients in each health state over the model time horizon

Abbreviations: IOP – Intraocular pressure

B6. Section B.3.3.2, Transition probabilities, page 111 & economic model sheet "clinical inputs", cells: "AZ29: BB29".

The company submission states that "*efficacy was assumed to be equivalent to a drug from the ITC within the same treatment class*". However, in the economic model, it is assumed that the transition probabilities for brinzolamide-brimonidine are equal to both dorzolamide-timolol and brinzolamide-timolol. However, these combinations belong to different treatment classes, with different mechanisms of

action. Please comment on the appropriateness of assuming equal transition probabilities in the model across different classes of treatment.

Original submission

As stated in Table 33 of Appendix J (replicated below in Table 25), the source of efficacy data (transition probabilities) for brinzolamide-brimonidine was the STC/MAIC (Kozobolis *et al*. [2017]), and this was not assumed to be equivalent to dorzolamide-timolol and brinzolamide-timolol.

As shown in Table 25, equivalence assumptions are applied for four comparators to comparators in the same drug class. These include assuming latanoprost-timolol, tafluprost-timolol, and travoprost-timolol are equivalent to bimatoprost-timolol, and assuming brinzolamide-timolol is equivalent to dorzolamide-timolol. Comparators in the same drug classes have an equivalent mechanism of action and are therefore expected to be of similar efficacy.[67]

'Transitions_ITC' cells A4 – P23 display the treatment effect results of the STC/MAIC for the comparators. In the base case, the treatment effects between brinzolamide-brimonidine and dorzolamide-timolol are not sufficiently different to shift any of the patients into different health states i.e., the STC results are applied separately for the two comparators but produce the same transition probabilities. However, sufficient variation is observed in the other sensitivity analyses (i.e., MAIC inputs) to observe changes in the transition counts.

Table 25: Original submission efficacy data sources (from Appendix J of original submission)

Comparator class	Comparator	Source of efficacy data
RKI + PGA	Netarsudil-latanoprost	MERCURY 3[6]
CAI + BB	Dorzolamide-timolol	STC/MAIC: Kozobolis *et al*. 2017[5]
	Brinzolamide-timolol	Assumed equivalent to dorzolamide-timolol
CAI + SYMP	Brinzolamide-brimonidine	STC/MAIC: Kozobolis *et al*. 2017[5]
SYMP + BB	Brimonidine-timolol	STC/MAIC: ODLASER[7]
PGA + BB	Bimatoprost-timolol	MERCURY 3[6]
	Latanoprost-timolol	Assumed equivalent to bimatoprost-timolol
	Tafluprost-timolol	

	Travoprost-timolol	

Abbreviations: BB – Beta-blocker; CAI – Carbonic anhydrase inhibitor; MAIC – matching-adjusted indirect comparison; PGA – Prostaglandin analogue; RKI – Rho-Kinase Inhibitor; STC – simulated treatment comparison; SYMP – Sympathomimetic

Updated submission (post-clarification questions)

Table 26 details the efficacy data sources for the comparators included in the updated ITC (replicated from Question A8). Changes to the original submission are highlighted in bold. The NMA-linked evidence has replaced the STC/MAIC links, as well as some of the within-class equivalency assumptions. As clarified in the table, equivalency assumptions are applied only to comparators in the same comparator class (brinzolamide-timolol equivalent to dorzolamide-timolol, and tafluprost-timolol to bimatoprost-timolol).

'Transitions_ITC_SE' cells A6 – E12 display the treatment effect results of the NMA for the comparators. In the NMA base case for the study eye and fellow eye, the treatment effects for all comparators are sufficiently different to always shift at least one patient into a different health state.

Table 26: Updated comparator efficacy data sources

Comparator class	Comparator	Source of efficacy data
RKI + PGA	Netarsudil-latanoprost	MERCURY 3[6]
CAI + BB	Dorzolamide-timolol	**NMA: Kozobolis *et al*. 2017[5] and Nixon et al. 2009[10]**
	Brinzolamide-timolol	Assumed equivalent to dorzolamide-timolol
CAI + SYMP	Brinzolamide-brimonidine	**NMA: Kozobolis *et al*. 2017[5], Katz et al. 2013[12] and Whitson et al. 2013[13]**
SYMP + BB	Brimonidine-timolol	**NMA: Nixon et al. 2009[10]**
PGA + BB	Bimatoprost-timolol	MERCURY 3[6]
	Tafluprost-timolol	Assumed equivalent to bimatoprost-timolol
	Latanoprost-timolol	**NMA: Rigollet et al. 2011[8]**
	Travoprost-timolol	**NMA: Rigollet et al. 2011[8]**

Abbreviations: BB – Beta-blocker; CAI – Carbonic anhydrase inhibitor; NMA – Network meta-analysis; PGA – Prostaglandin analogue; RKI – Rho-Kinase Inhibitor; SYMP – Sympathomimetic

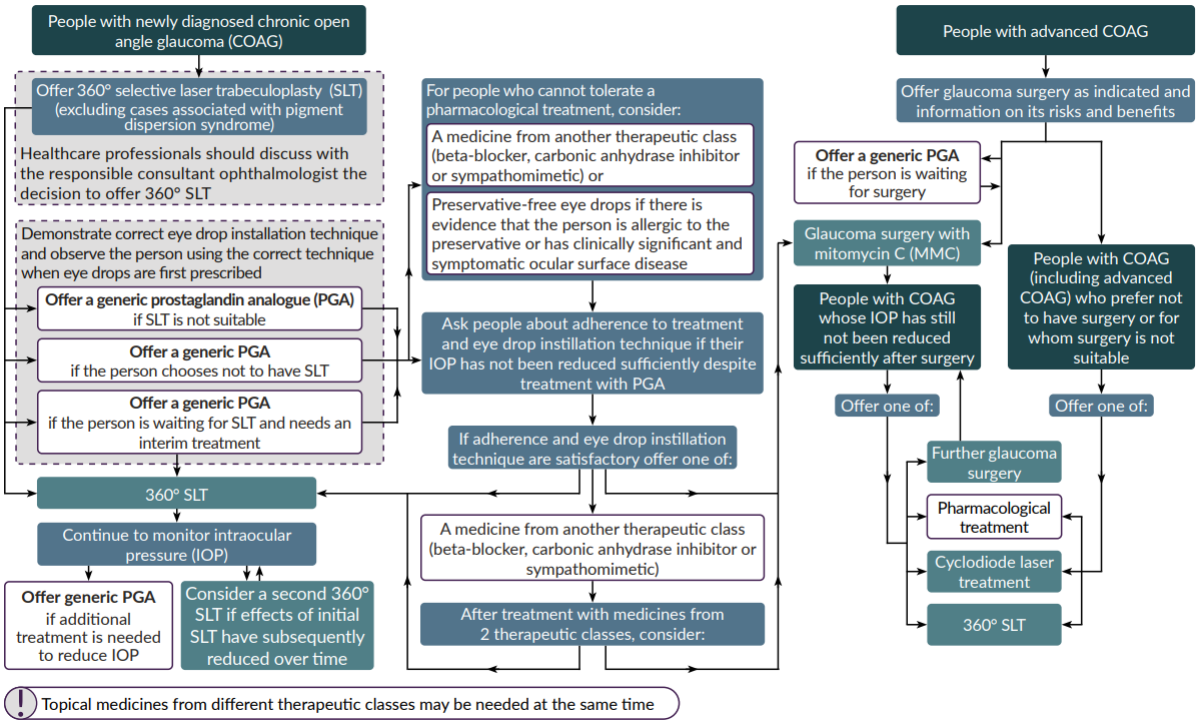
Treatment discontinuation

B7. PRIORITY. Section B.3.3.4, Treatment discontinuation, page 115 & economic model Markov traces.

We are concerned that the model output lacks face validity. Once the cohort discontinues treatment, the model does not include any further lines of treatment. This assumption does not reflect treatment in UK clinical practice, where further lines of treatment and/or surgery would be provided to reduce IOP. It is further assumed that treatment discontinuation does not impact on health state occupancy (i.e., once the cohort comes off treatment, there is no impact on IOP). These assumptions lead to model output that lacks face validity. For example, treatment discontinuation increases QALYs through a reduction in adverse event disutilities, but there are no QALY losses associated with increases in IOP. This can be seen on the model traces (e.g., Roclanda Markov trace) where at year 5, [redacted] of the cohort are in the 20-30% or >30% IOP reduction states, despite only [redacted] of patients remaining on treatment. The implication of the modelling approach is that the most cost-effective use of combination therapy is to discontinue immediately. Please revise the model to ensure more plausible model outputs. This could be achieved through modelling the treatment acquisition costs of future treatment lines and modelling the impact of treatment discontinuation on IOP, and subsequently the risk of glaucoma disease progression (see Question B2 above).

Functionality has been added in the model to incorporate a second line of treatment for patients discontinuing. The model contains functionality to allow for user variation of the composition of the post discontinuation basket. The base case results assume that initially discontinued patients will accrue an average cost of all available treatments, weighted market share value, and redistributed to account for the removal of the product they are discontinuing from. Following this, patients will move to a weighted cost of generic PGAs – as per disease management guidance to give patients who fail treatment generic PGAs (Figure 17). As data for the time, it take patients to move to generic PGAs is not available, the model assumes this shift occurs at the median point of the modelled time horizon (16.4years). This means, in the base case, post discontinuation patients are administered an average cycle cost shown in Table 12.

Figure 17: Management options for patients with POAG[33]



Note: Chronic open-angle glaucoma is another term used for POAG.

Abbreviations: COAG – chronic open-angle glaucoma; IOP – intraocular pressure; MMC – mitomycin C; PGA – prostaglandin analogue; POAG – primary open-angle glaucoma; SLT – selective laser trabeculoplasty

Table 27: Variation in the weighted cost following discontinuation

Intervention	Average cost per cycle, post discontinuation		
	Base case	**No shift to generics**	**Immediate shift to generics**
Netarsudil-latanoprost	£14.77	£12.89	£14.51
Brinzolamide & Timolol	£14.81	£13.68	£14.51
Dorzolamide & Timolol	£14.85	£13.81	£14.51
Latanoprost & Timolol	£15.25	£13.03	£15.28
Tafluprost & Timolol	£14.76	£12.94	£14.51
Bimatoprost & Timolol	£8.30	£10.50	£6.30
Travoprost & Timolol	£14.77	£12.99	£14.55
Brinzolamide & brimonidine	£14.79	£13.17	£14.51
Timolol & Brimonidine	£14.75	£12.99	£14.51

The replacement comparator is associated with a weighted cost using a weighted average of 5-year market share, assuming year 5 is the LOCF for the remainder of the

CE time horizon. It is assumed that patients do not receive the same comparator after discontinuing i.e., the replacement comparator omits the current treatment regimen.

The unit costs for the second line comparator (i.e., after discontinuation) are equivalent to those for patients who receive the comparator in first line (using product market share-weighted acquisition costs, administration costs, and compliance considerations). SLT and trabeculectomy treatments are applied independent of intervention/comparator treatment for all patients as one-off costs and are therefore not impacted by treatment discontinuation.

As detailed in Section B.2.9.2.3 of Document B, prior treatment was not identified as a treatment effect modifier or prognostic variable in the targeted literature search or by the clinical expert. This notion is supported by the IPD from MERCURY 3, in which the IOP of discontinuing patients was notably larger than on the patients continuing in the trial (Table 28). Accordingly, patient health state transitions in the second line are equivalent to the first line transitions.

Updated base case results are presented in Table 89 of Appendix D.

Table 28: IOP of continuing and discontinuing patients

	Netarsudil-latanoprost		Bimatoprost-timolol	
Patient group	Continuing	Discontinued	Continuing	Discontinued
Observation number	1745	40	1842	4
IOP, mmHg mean (SD)	15.6 (3.24)	18.0 (4.10)	15.3 (2.92)	18.0 (5.89)
IOP, mmHg median (min, max)	15.5 (7.0, 29.5)	16.8 (10.5, 28.0)	15.0 (8.0, 27.0)	19.0 (10.0, 24.0)

Abbreviations: IOP – Intraocular pressure; Max – Maximum; Min – Minimum; SD – Standard deviation

B8. PRIORITY. Section B.3.3.4, Treatment discontinuation, page 115.

Treatment discontinuation rates for all comparators (except netarsudil-latanoprost) are assumed equal to bimatoprost-timolol. Please provide evidence to support this assumption. Broadening the systematic review of clinical effectiveness evidence as described in Section A above should provide additional data on treatment discontinuation that could be incorporated into the economic model.

As detailed in the response to question A2, targeted searches were conducted for clinical, economic, HRQoL, and cost and resource use studies for all time up to 2017.

Four relevant studies (see Table 29) were identified as containing information on treatment discontinuation and screened for incorporation into the model. The updated treatment discontinuation sources and values are detailed in Table 29. Bolded values represent changes from the original submission. Where multiple sources were available, options were added to the model for different discontinuation selections to be made. The base case settings were conservatively selected based on lower rates of discontinuation (higher rates of persistence).

In line with the procedure for the MERCURY 3 calculation as detailed in section B.3.3.4 of the original submission, the number of patients discontinuing in the trial period was translated to a proportion dependent on the total number of patients, before dividing by the number of cycles in the trial and converting to a rate for the treatment arms separately. As described in Question B9, in line with clinician input, extrapolations were applied for all comparators, based on the proportional change in MERCURY 3 from month 1 to the remaining months.

Updated base case results are presented in Table 89 of Appendix D.

Table 29: Comparator discontinuation data source

Comparator class	Comparator	New source of discontinuation data	New rate per cycle	Previous rate per cycle	Difference
RKI + PGA	Netarsudil-latanoprost	MERCURY 3[6]	[redacted]	[redacted]	0.0000000
CAI + BB	Dorzolamide-timolol	**Nixon et al., 2009 (base case)**[10]	**0.9727**	0.9895	0.0168000
		Sall et al., 2003 (setting)[11]	**0.9594**	0.9895	0.0301000
	Brinzolamide-timolol	**Assumed equivalent to dorzolamide-timolol**	**See above**	0.9895	n/a
CAI + SYMP	Brinzolamide-brimonidine	**Katz et al., 2013 (base case)**[12]	**0.9700**	0.9895	0.0195000
		Whitson et al., 2013 (setting)[13]	**0.9011**	0.9895	0.0884000
SYMP + BB	Brimonidine-timolol	**Nixon et al., 2009 (base case)**[10]	**0.9533**	0.9895	0.0362000
		Sall et al., 2003 (setting)[11]	**0.9431**	0.9895	0.0464000
PGA + BB	Bimatoprost-timolol	MERCURY 3[6]	0.9895	0.9895	0.0000000
	Latanoprost-timolol	Assumed equivalent to bimatoprost-timolol	0.9895	0.9895	0.0000000
	Tafluprost-timolol		0.9895	0.9895	0.0000000
	Travoprost-timolol		0.9895	0.9895	0.0000000

Abbreviations: BB – Beta-blocker; CAI – Carbonic anhydrase inhibitor; MAIC – matching-adjusted indirect comparison; n/a – not available; PGA – Prostaglandin analogue; RKI – Rho-Kinase Inhibitor; SYMP – Sympathomimetic

B9. PRIORITY. Section B.3.3.4, Treatment discontinuation, page 115.

Please provide full details of the reasons for treatment discontinuation observed in the MERCURY 3 trial for both treatment arms (including both discontinuation for adverse events and other reasons). Please comment on whether the reasons for treatment discontinuation are likely to reflect treatment discontinuation in UK clinical practice.

If the reasons for treatment discontinuation are predominantly adverse event related, and if adverse events occur mainly in early cycles of treatment, it may not be appropriate to assume a continuous treatment discontinuation rate extrapolated over the full model time horizon. Please explore alternative treatment discontinuation assumptions with clinical experts and integrate the findings into a revised economic model analysis.

The reasons for treatment discontinuation observed in the MERCURY 3 trial are presented in Table 30. The main reason for subject discontinuation in MERCURY 3 was discontinuation due to adverse events (DDTAE); 18.3% and 1.9% of patients in the netarsudil-latanoprost and bimatoprost-timolol treatment arms discontinued treatment due to adverse events, respectively.[6] It is expected that the main reason for treatment discontinuation in UK clinical practice will be DDTAE. The remaining reasons for discontinuation in MERCURY 3 were largely related to protocol deviations and withdrawal of consent.

Table 30. Reasons for subject discontinuation in MERCURY 3[6]

Reason for subject discontinuation	Netarsudil-latanoprost QD (N=218), n (%)	Bimatoprost-timolol QD (N=212), n (%)
Adverse event	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Non-compliant	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]
Disallowed concurrent medication	[redacted]	[redacted]
Investigator decision	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]
Death	[redacted]	[redacted]
Other	[redacted]	[redacted]

Abbreviations: QD – Once daily

In the CEM, discontinuation rates were sourced from comparator studies where available. Where rates were not sourced, comparators in the same class were used as proxies, assuming that discontinuation within comparator classes is comparable.

Clinicians suggested that the discontinuation rate is expected to remain generally consistent over time, aside from the short term (~1st month) that reflects cosmetic changes (e.g., fat atrophy, increased periorbital pigment, lash growth, allergic reaction).

Where IPD were available, in line with suggestions of clinicians, data has been separated into a month 1 discontinuation rate and a separate rate for the remaining trial period, which is applied for the treatment horizon. As IPD were not available for comparators, trial-reported rates are applied for the length of the respective trial, with an extrapolation multiplier applied to the rate for the remaining treatment horizon. This extrapolation multiplier is based on the percentage change from month 1 to the remaining MERCURY 3 periods, for netarsudil-latanoprost and bimatoprost-timolol.

Table 31 displays the rates applied for each comparator in the model. As detailed in Question B8, several new sources have now been utilised for discontinuation rates, including sensitivity analyses in the model to vary some rates.

Updated base case results are presented in Table 89 of Appendix D. A sensitivity analyses varying the source of discontinuation/persistence rates is displayed in Table 135. Results are largely unimpacted, with no notable change in the ICERs of comparators; netarsudil-latanoprost remains dominated by five comparators, dominating two, and one positive ICER around £20,000 is present for tafluprost-timolol.

Table 31: Comparator discontinuation data source

Comparator class	Comparator	New source of discontinuation data	Reported trial rate	Cycle number applied for:	Rate applied thereafter
RKI + PGA	Netarsudil-latanoprost	MERCURY 3[6]	[redacted]	1	[redacted]
CAI + BB	Dorzolamide-timolol	Nixon et al., 2009 (base case) or Sall et al., 2003 (setting)[10,11]	0.9727 or 0.9594	3	0.9674 or 0.9514
	Brinzolamide-timolol	Assumed equivalent to dorzolamide-timolol	0.9727 or 0.9594	3	0.9674 or 0.9514
CAI + SYMP	Brinzolamide-brimonidine	Katz et al., 2013 (base case) or Whitson et al., 2013 (setting)[12,13]	0.9700 or 0.9011	3	0.9642 or 0.8804
SYMP + BB	Brimonidine-timolol	Nixon et al., 2009 (base case) or Sall et al., 2003 (setting)[10,11]	0.9533 or 0.9431	3	0.9441 or 0.9317
PGA + BB	Bimatoprost-timolol	MERCURY 3[6]	0.9952	1	0.9932
	Latanoprost-timolol	Assumed equivalent to bimatoprost-timolol	0.9952	1	0.9932
	Tafluprost-timolol		0.9952	1	0.9932
	Travoprost-timolol		0.9952	1	0.9932

Abbreviations: BB – Beta-blocker; CAI – Carbonic anhydrase inhibitor; PGA – Prostaglandin analogue; RKI – Rho-Kinase Inhibitor; SYMP – Sympathomimetic

Health state utility values

B10. PRIORITY. Section B.3.4.1, HRQoL data from clinical trials.

In the submission, utilities are derived from mapping SF-36 data from the MERCURY 3 trial to EQ-5D utilities in line with the NICE reference case. However, mapping inevitably introduces uncertainty. To mitigate this uncertainty, please provide the following:

- SF-6D health state utility values (mean, SE, N) using the available trial data.
- An estimate of treatment effect size on SF-6D utilities.
- Health states utility values defined using absolute mean IOP, as well as change in IOP from baseline.

Please provide scenario analyses using health state utility values based on SF-6D utility data.

In the submission, the SF-36 quality of life data were mapped to EQ-5D in line with the NICE reference case as stated in TSD22[68]. As stated in the question, as mapping utility data creates uncertainty, providing another mapping method is an unsuitable solution to these concerns. Given that mapping to SF-6D is less commonly used, with the previously provided NICE reference case[68] of mapping to EQ-5D most often used in the literature, to address these concerns we have provided the input data for the existing mapping and compared to the EQ-5D data used in the model. The SF-36 data has been converted to match the six categories in the SF-6D method, as undertaken in the EQ-5D mapping, creating mean values for all patients.

The SF-6D health state mean values from the MERCURY 3 trial are presented in Table 32 and Table 33. The physical health summary measure consists of the Physical Functioning, Role Physical, Bodily Pain, and General Health scales. The mental health summary measure consists of the Vitality, Social Functioning, Role Emotional, and Mental Health scales. The Reported Health Transition scale is not included in either of the summary measures as the scale was not utilised for mapping. Patients who did not report data for any of the scales presented in each summary measure at Visit 9 were not included.

The mean values at Visit 9 would be expected to increase with increasing IOP percentage reduction thresholds across the health states. This is observed in the mental health summary measure but not for the physical health summary measure. This unexpected trend could be due to the smaller sample size of patients in the 20-30% health state, as well as the fact that values are not presented by treatment arm so treatment effect cannot be accounted for. However, the trend in mean values across health states is largely consistent and the differences are not considerable, as supported by the results that no statistically significant difference was found between the mean values at Visit 9 across the health states after an ANOVA test was conducted (p=0.233 for the physical health summary measure and p=0.800 for the mental health summary measure).

In the submission, health state utility values presented were defined by the percentage change in IOP, as this was considered to be a more accurate reflection of UK clinical practice while accounting for variability between trials (see response to Question A9.). Hence, health states utility values defined using absolute mean IOP are not appropriate to provide.

Table 32: SF-6D mean values for physical health summary measure (Physical Functioning, Role Physical, Bodily Pain, General Health)

Health state	N at visit 9	Mean SF-6D value at Visit 1 (SE)	Mean SF-6D value at Visit 9 (SE)
<20%	2789	2.994 (1.059)	3.011 (1.054)
20-30%	2056	-	2.997 (1.058)
>30%	2667	-	3.013 (1.041)

Abbreviations: SE – Standard error; SF-6D – Short Form Six-Dimension

Table 33: SF-6D mean values for mental health summary measure (Vitality, Social Functioning, Role Emotional, Mental Health)

Health state	N at visit 9	Mean SF-6D value at Visit 1 (SE)	Mean SF-6D value at Visit 9 (SE)
<20%	1862	3.397 (1.271)	3.387 (1.266)
20-30%	1370	-	3.406 (1.288)
>30%	1776	-	3.421 (1.255)

Abbreviations: SE – Standard error; SF-6D – Short Form Six-Dimension

Table 34 and Table 35 show the mean difference in SF-36 mean values from Visit 1 to Visit 9 by treatment arm, with the physical health and mental health summary measures. The treatment effect of bimatoprost-timolol appears to be greater than that of netarsudil-latanoprost. However, the variation is negligible, with no statistically

significant difference in mean values at Visit 9 between both treatment arms after conducting an independent t-test (p=0.0793 for the physical health summary measure and p=0.828 for the mental health summary measure).

Table 34: SF-36 mean values for physical health summary measure (Physical Functioning, Role Physical, Bodily Pain, General Health)

Treatment arm	N at Visit 9	Mean value at Visit 1 (SE)	Mean value at Visit 9 (SE)	Mean difference in values from Visit 1 to Visit 9
Netarsudil-latanoprost	3360	3.006 (1.089)	2.977 (1.081)	-0.0293
Bimatoprost-timolol	4152	2.981 (1.026)	3.013 (1.038)	0.0320

Abbreviations: SE – Standard error; SF-36 – 36-Item Short Form Survey

Table 35: SF-36 mean values for mental health summary measure (Vitality, Social Functioning, Role Emotional, Mental Health)

Treatment arm	N at Visit 9	Mean value at Visit 1 (SE)	Mean value at Visit 9 (SE)	Mean difference in values from Visit 1 to Visit 9
Netarsudil-latanoprost	2239	3.405 (1.279)	3.410 (1.258)	0.00528
Bimatoprost-timolol	2769	3.390 (1.263)	3.400 (1.276)	0.00993

Abbreviations: SE – Standard error; SF-36 – 36-Item Short Form Survey

B11. PRIORITY. Section B.3.4.2 "Mapping", page 116 & Appendix M3 "Estimation of health state utility values via mapping" page 214.

We recognise that the mapping to EQ-5D health state utility values is in line with the NICE reference case. However, mapping is associated with a certain degree of uncertainty and the potential risk of introducing bias into the evaluation. Please provide further details of the mapping approach taken, following the recommendations of NICE TSD 22 (previously NICE TSD 10). Please provide full details of how the TSD recommendations were followed, with a detailed description of any deviations from the recommended approach.

Given that NICE TSD 22 was not published within reasonable time before the date of the submission (June 2023, alike the submission), the NICE TSD 10 document was referred to when the mapping of HRQoL data from SF-36 to EQ-5D was conducted. However, the NICE TSD 22 documents have since been reviewed to ensure alignment with latest NICE guidance where possible, as detailed below.

Data availability in MERCURY 3

In the MERCURY 3 trial, SF-36 data was collected and not EQ-5D, as described in Document B.2.2 and B.2.3. NICE TSD 22 states: “when EQ-5D data is not available, this data can be estimated by mapping other health-related quality-of-life measures or health-related benefits seen in the relevant clinical trials to EQ-5D.” Mapping was conducted to map SF-36 to EQ-5D, which follows this recommendation from TSD 22.

NICE TSD22 also states that “for mapping to be a relevant tool, or indeed for the use of EQ-5D derived by any method to be considered relevant, there must be a plausible relationship between the clinical measure(s) and EQ-5D. This is often referred to as conceptual overlap.” For the mapping in the submission, Table 36 displays how the eight dimensions of the SF-36 measure generally correspond to the five-dimensions of the EQ-5D measure. A high level of similarity can be observed across the two measures, demonstrating ‘conceptual overlap’.

Table 36: EQ-5D and SF-36 dimensions

EQ-5D dimensions	SF-36 dimensions
Mobility	Physical functioning
Self-care	General health perception, role limitations due to physical health, role limitations due to emotional problems, social functioning, vitality
Usual activities	
Pain/discomfort	Pain
Anxiety/depression	Mental health

Abbreviations: EQ-5D – EuroQol Five Dimension; SF-36 – 36-Item Short Form Survey

Identification of the algorithms

A targeted literature review was undertaken to identify the most appropriate algorithm to perform the mapping. Four potentially relevant algorithms were identified which were reported in the HERC database of mapping studies[69] (Ara and Brazier (2008)[67], Kim *et al*. (2014)[71], Maund *et al.* (2012)[72] and Rowen *et al*. (2009)[73]).

Assessment of the algorithms

Though none of the algorithms were developed from datasets of patients with specific eye-related diseases, they were considered appropriate for consideration. In alignment with NICE TSD 10 and 22 guidance, Ara and Brazier (2008)[70] and Rowen et al. (2009)[73] were considered most appropriate for this analysis, as these algorithms were developed using datasets collected in the UK and included patient observations

with various indications. This is expected to be inclusive of a range of disease states, including patients within the MERCURY 3 trial. Applicability and reliability of these algorithms was also demonstrated by the comparatively larger number of observations (Ara and Brazier (2008)[70]: 6,350; Rowen *et al.* (2009)[73]: 33,248; Kim *et al.* (2014)[71]: 1,660; Maund *et al.* (2012)[72]: 133). The Ara and Brazier (2008) method has previously been accepted by NICE in HST5.[74,75] In line with the recommendations of TSD 22, these algorithms are inclusive of all patients in the model, covering all health states for the entire time horizon.

The Ara and Brazier (2008)[70] publication utilised data from 12 clinical trials, aligning with the NICE TSD 22 recommendations that "clinical trials may offer advantages in terms of data quality and consistency of outcome definitions with the evidence of treatment effect." Rowen *et al.* (2009)[73] used data collected from a prospective survey of inpatients and outpatients, and was therefore, considered as a sensitivity analysis in the model.

Both publications used a variety of models to estimate the relationship between SF-36 and EQ-5D. The EQ(1) model was selected from Ara and Brazier (2008) as it was identified as having the best predictive power for EQ-5D; the root mean squared error, recommended for assessment of model performance by TSD 10, was 0.1832. The third random-effect GLS model was used from Rowen *et al*. (2009)[73], which based on measure of fit, assessed how well the data fitted the model and how accurately the model predicted EQ-5D. This model had mean squared error of 0.030, the lowest of the models in the paper. Furthermore, in fulfilment with TSD 22, both Ara and Brazier (2008)[70] and Rowen *et al.* (2009)[73] use plots of predicted EQ-5D against actual values for evaluation.

The inclusion of age in the mapping model was not previously specified in NICE TSD 10 but is now recommended in NICE TSD 22. Neither publication included age as a covariate in the model and therefore, age was not included when estimating HSUVs. However, the utilities estimated using the Ara and Brazier (2008)[70] mapping algorithm were in line with the existing utility values in the published literature, with similar mean ages (NICE HST5.[74,75]).

In line with the recommendations of TSD 22, the Ara and Brazier (2008)[70] publication evaluated the appropriateness/closeness of predictions to the actual EQ-5D values,

using several methods. Numerical and visual evaluation included the proportion of variance explained, the difference in actual and predicted means, absolute errors, distribution of errors and several other metrics.

Utilities and uncertainty

In line with NICE TSD 10 and TSD 22, sensitivity analyses were presented to explore variation in using mapping algorithms on the outputs. The uncertainty was explored through a PSA and in an one-way sensitivity analysis (OWSA), where a 20% variance was assumed. Additionally, in accordance with NICE TSD22 guidance, a sensitivity (scenario) analysis using an alternative mapping algorithm published in Rowen *et al.* (2009)[73] was used. All analyses demonstrated that mapping of utilities did not have a significant impact on the cost-effectiveness of netarsudil-latanoprost.

Updated base case results are presented in Table 89 of Appendix D. The sensitivity analyses varying the mapping algorithm is displayed in Table 142. The results of the sensitivity were highly sensitive to changes in the mapping algorithm. When the alternate algorithm was applied, netarsudil-latanoprost dominated brinzolamide-brimonidine, dorzolamide-timolol, bimatoprost-timolol, brimonidine-timolol and brinzolamide-brimonidine, which was the opposite in the deterministic base case results.

B12. PRIORITY. Section B.3.4.3, HRQoL studies, pages 116-117.

Please update the HRQoL searches to include studies pre-2017 and provide a full report of all health state utility values used in previous economic models. Please provide a scenario analysis using UK EQ-5D-based utilities obtained from the literature. These should be aligned with any updates to the model provided in response to query B2 above.

As detailed in the response to Question A2, targeted searches were conducted for clinical, cost-effectiveness, HRQoL, and cost and resource use studies for all time up to 2017.

The PRISMA diagram in Figure 2 (in response to Question B1) summarises the screening of economic publications through each stage of the targeted database searches. As described in the PRISMA, 121 unique references met the criteria for the

full text review stage. Following the review of full texts, a total of 94 publications were excluded as they did not meet the selection criteria, leaving 27 publications. Of these 27 publications, 5 publications met the selection criteria for the HRQoL review, and were data extracted.

Please see Table 65 and Table 66 in Appendix A of this document for a summary of the HRQoL publications identified as part of the targeted searches.

As previously outlined in the response to Question B2 above, we consider the current model structure to be most appropriate. Within this structure, two scenario analyses using UK EQ-5D-based utilities have been included based on the findings of the economic targeted searches (Table 37). Stein *et al.* 2012[51] and Orme *et al.* 2012[41] were identified as providing glaucoma utility values analogous to the model health states and structure. The mild, moderate, and severe utility values from the papers were applied to the >30%, 20-30%, <20% IOP reduction health states, respectively. Where standard error was not reported, proxy values from the base case (MERCURY 3 mapping) were used.

Updated base case results are presented in Table 89 of Appendix D. The sensitivity analyses varying health state utility values are displayed in Table 143. The sensitivity analyses results for the scenarios using Stein *et al.* (2015) and Orme *et al.* (2012) utility values were largely similar. Relative to netarsudil-latanoprost, for the Stein *et al.*-based utilities scenario, latanoprost-timolol and travoprost-timolol were the dominating treatments while only travoprost-timolol was the dominating treatment in the Orme *et al.*-based utilities scenario. Treatments in the Orme *et al.* scenario were associated with worse incremental QALYs. Results from the two scenarios vary from the base case, with the ICER against netarsudil-latanoprost for tafluprost-timolol decreasing in both, while latanoprost-timolol increases to a positive ICER in the Orme *et al.*-based scenario and becomes a dominating treatment in the Stein *et al.*-based scenario.

Table 37: Scenario analyses utility values sourced from the TLR

Study	Glaucoma utility values [SE]
MERCURY 3 mapping (base case)	<20% reduction in IOP: 0.805 [0.007] 20-30% reduction in IOP: 0.816 [0.017] >30% reduction in IOP: 0.822 [0.015]

Stein *et al*. (2012)[51], from Lee (2007)	Mild: 0.92 [0.13] Moderate: 0.89 [0.22] Severe: 0.86 [0.30]
Orme *et al*. (2012)[41], from Brown (2003)	Mild: 0.78 [NR]* Moderate: 0.72 [NR] Severe: 0.61 [NR]

Abbreviations: NR – Not reported; SE – Standard error; LR – Targeted literature review
*Age specific utilities were provided for the mild health state. The 65-74 years old range was chosen based on the patient age at baseline in the model (67.2 years), based on the mean from the MERCURY 3 trial.

Costs and resource use

B13. PRIORITY. Section B.3.5.1, Intervention and comparators' costs and resource use, page 120.

Treatment acquisition costs for intervention and comparators are all based on "intended use" and assume treatment in both eyes. Please provide the following information:

A) Please confirm what proportion of participants in the MERCURY 3 and other studies had treatment in both eyes?
B) Please confirm (and provide evidence) that the treatment of two eyes is standard practice in the UK.
C) Please provide details of mean (SD) dosing from each arm of the MERCURY 3 trial, and from other studies included in the ITC where available.
D) Please provide a scenario analysis using the mean dosage as the basis for treatment acquisition cost calculation.

A) All patients (100%) in MERCURY 3 received treatment in both eyes, though primary analysis presented data on only the 'study eye' and data for both eyes were not pooled for presentation. However, fellow eye data are presented for some outcomes in the CSR. A previous pharmaceutical company, Aerie, conducted the MERCURY 3 study and wrote the CSR without stating explicitly which eye was to be the selected study eye. The IPD suggests that IOP, central corneal thickness, visual field mean deviation, and cup-disk ratio IPD were used in the study eye selection process, where it appears the 'worst-seeing eye' was favoured.

Original submission

In both Kozobolis *et al*. (2017) and ODLASER only one eye from each patient was included/eligible for the study. In ODLASER, this was the worst-seeing eye (defined by the higher baseline IOP).

Updated submission (post- clarification questions)

Table 45 in the response to Question B18 details which comparator studies reported information on both 'study eye' and 'fellow eye'. Alike MERCURY 3, in four comparator trials 100% of patients received treatment in both eyes.[10,14–16] Rigollet *et al*. (2011) did not report the proportion of patients that received treatment in both eyes and Kozobolis *et al*. (2017) included only one eye in the study.[5,8] In the two remaining studies, Katz *et al*. (2013) and Whitson *et al*. (2013), patients could enter the study with one or two eyes, if both met the inclusion criteria.[12,13] However, the proportion of patients that received treatment in both eyes was not reported. Despite the variation observed, all studies (except DuBiner *et al*. [2011]) based primary efficacy data on one 'study eye' and safety analysis on both eyes.

B) Treatment in both affected eyes is standard practice in the UK. The summary of product characteristics for brinzolamide and travoprost, netarsudil-latanoprost, bimatoprost and timolol, and brimonidine and timolol each reference the recommendation to use the product in the affected "eye(s)", indicating treatment of both eyes is common practice. In clinical practice, unit dose presentations are also typically half the size of batch dose products, with a unit dose fill volume providing enough dosage to treat two eyes. NHS glaucoma guidelines[33] do not explicitly refer to whether treatment is typically one or both eyes.

C) The mean dosage in MERCURY 3 was not reported. All patients were assigned an equal dose (one drop in each eye, once a day between 20:00 and 22:00) and treatment duration. Consequently, variance between the assigned and mean dose were driven by lack of compliance and treatment discontinuation. All the comparators in the model apply the same principle, with the same generic dose for all patients receiving treatment with each comparator.

MERCURY 3 compliance

As stated in the MERCURY 3 CSR, no formal record of treatment compliance was planned, with cases of treatment non-compliance recorded as protocol deviations. In MERCURY 3 doses were administered by the study subjects, who were provided with a paper and electronic dosing reminder. If a dose of study medication was missed the subject was to take the next dose as planned, and a minor protocol deviation was recorded. As shown in Table 38, protocol deviations occurred in [redacted]% of subjects, with similar rates seen for both netarsudil-latanoprost ([redacted]%) and bimatoprost-timolol ([redacted]%).

MERCURY 3 discontinuation

Displayed in Table 39, discontinuation rates in both arms were generally minimal and equal across the treatment arms. The only exception to this is discontinuation due to AEs, which caused [redacted]% of netarsudil-latanoprost patients to discontinue.

Mean dosage: comparators in the original submission

For the comparator trials in the original submission, mean dosage was not available. ODLASER included “a change in dosage” as part of the exclusion criteria, while Kozobolis *et al*. (2017) did not clarify the approach to dosage.

Mean dosage: comparators in the updated submission (post- clarification questions)

Mean dosage was not reported for any of the comparator trials in the updated submission. See the response to Question A8 (treatment arm heterogeneity subsection) for a comparability assessment of the treatment arms in the NMA that were assessed in multiple studies (netarsudil-latanoprost, latanoprost, brimonidine, brinzolamide-brimonidine, brinzolamide and dorzolamide-timolol). For all FDC comparators, except brinzolamide-brimonidine, the dose administration and regimens were equivalent across studies. For brinzolamide-brimonidine, variation existed in the frequency of administration in Kozobolis *et al*. (2017) (twice daily rather than three times daily in Katz *et al*. [2013] and Whitson *et al*. [2013]).[12,13] This was permitted for the NMA since in the literature,

recommendations permit the use of brinzolamide-brimonidine two to three times daily.[19–21] Additionally, the dose frequency in each of the trials was consistent with the dosing regimen recommended for the study location; see the response to Question A8 for further details.

Table 38: MERCURY 3 protocol deviations, randomised population (N=430)

Protocol deviations	Netarsudil-latanoprost	Bimatoprost-timolol	All subjects
Any deviations	[redacted]	[redacted]	[redacted]
COVID-19 related deviations	[redacted]	[redacted]	[redacted]
Major deviations	[redacted]	[redacted]	[redacted]
COVID-19 related major deviations	[redacted]	[redacted]	[redacted]
Minor deviations	[redacted]	[redacted]	[redacted]
COVID-19 related minor deviations	[redacted]	[redacted]	[redacted]

Table 39: MERCURY 3 reason for subject discontinuation, randomised population (N=430)

Reason for subject discontinuation	Netarsudil-latanoprost	Bimatoprost-timolol	All subjects
Adverse events	[redacted]	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]	[redacted]
Non-compliant	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]
Disallowed concurrent medication	[redacted]	[redacted]	[redacted]
Investigator decision	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]

Considering the lack of availability of mean dosage data across the comparator trials, outlined in the Question B13.C response, the inclusion of mean dosage in the acquisition cost calculation is unfeasible. The acquisition cost calculation in the model currently applies the assigned dosage (1 drop a day per affected eye) and compliance (assumed 100%). As clarified in the Question B13.C

response, any variance between the assigned and mean dose were driven by a lack of compliance or treatment discontinuation. Treatment discontinuation is modelled in the cost calculations, while compliance is assumed to be 100% for all comparators.

B14. Section B.3.5.1, Intervention and comparators' costs and resource use, pages 120-123.

Please provide a table that compares the costs of all comparator treatments using the weighted average based on market share data vs. the lowest-cost drug within each class. Please provide a scenario analysis applying the lowest-cost drug within each class.

Table 40 displays the base case costs (using a weighted average based on market share data) and scenario costs (using the cheapest product within each class). The cost per cycle and total costs in the scenario reduces for all comparators (ranging from a £38 reduction to £607 reduction). Table 147 in Appendix D displays the full scenario results. In the scenario relative to netarsudil-latanoprost, costs decrease for most comparators, while QALYs remain largely unchanged. Consequently, two comparators dominated by netarsudil-latanoprost in the base case become positive ICERs, the ICER for tafluprost and timolol increases, and the remaining ICERs remain unchanged.

Table 40: Comparator costs using market share weights vs. lowest-cost drug within each class

	Weighting	Total cost per cycle (£)		Total cost - per patient across patient lifetime (£)		
		Market shares weighted average	Lowest-cost within class	Market shares weighted average	Lowest-cost within class	Difference
Netarsudil-latanoprost	Existing	£14.51	NA	£13,075	£13,002	-£73
Brinzolamide-timolol	Generic 10MG/5ML*: 100%	£7.34	£3.86	£12,654	£12,491	-£163
Travoprost-timolol	Generic 2.5ml: 100%	£12.18	£5.49	£13,277	£12,670	-£607
Dorzolamide-timolol	Generic: Dorzolamide and timolol ZVA 5ml: 100%	£9.56	£2.07	£12,746	£12,477	-£269
Latanoprost-timolol	Generic: Latanoprost and timolol 2.5ml: 100%	£12.22	£6.33	£13,128	£12,604	-£524
Tafluprost-timolol	Existing	£14.71	NA	£13,274	£13,236	-£38
Bimatoprost-timolol	Timozva and bimatoprost 3ml: 100%	£15.82	£15.32	£12,462	£12,226	-£236
Brimonidine-timolol	Combigan 5ml: 100%	£13.74	£12.18	£12,813	£12,713	-£100
Brinzolamide-brimonidine	Existing	£11.24	NA	£12,750	£12,680	-£70

*Brinzolamide 10 mg per 1 ml, Timolol (as Timolol maleate) 5 mg per 1 ml
Abbreviations: ml – Millilitres; NA – not available

B15. Section B.3.5.1, Intervention and comparators' costs and resource use, pages 120-123.

In the base case economic model, there is inconsistent use of NHS indicative pricing or tariff pricing. Please provide further details and justification for the choice of each comparator price applied in the base case economic model. Please update the base case model if required to align with the NICE reference case.

Due to the unique nature of ophthalmology and "brand loyalty" amongst patients and prescribers, to use the standardised approach of the lowest available cost on the BNF does not apply. Instead, the base case of the model is set so that all generic products use the cheapest available BNF drug tariff price, whereas all branded products to use NHS indicative price relative to the product's specific manufacturer and brand on the basis that in real world practice doctors prescribe brand name products, as opposed to generic drug names. NICE guidance, NG81, supports this through stating that non-generics should be prescribed to those not tolerating generic products.[33]

To confirm which products are based on either the NHS indicative price or the drug tariff price, please see the table in rows 996:1037 in the Data Store of the originally submitted model.

As discussed in Question B14, a scenario is explored in the model, using the lowest-cost product within each class. This is detailed in Table 147 of Appendix D.

B16. Section B.3.5.1, Intervention and comparator cost and resource use, page 120.

Please clarify whether there is any consideration of wastage within the treatment acquisition costs? Please confirm whether the shelf life of all treatments included in the model is sufficiently long to ensure that no treatment wastage occurs.

A switch to include or exclude wastage for the intervention/comparators is now included on the 'Settings' tab of the CEM. The base case of the updated model includes wastage.

When included, wastage is captured as part of the cost per drop for all comparators and the intervention. The expiry once opened for each comparator/intervention is

considered, comparing the pack size with the dosage within the expiry-life timeframe. Assuming that the remaining product is wasted at the end of the expiry-life, a proportion of wasted product is calculated and the price per drop is increased by this proportion. This is calculated for each product within each comparator class and the within-class market share weighting is applied as detailed in Document B Section 3.5.1.

In line with the assumption of 100% compliance, detailed in Section B.3.3.4 of Document B, wastage for all comparators is calculated assuming no missed doses or lost/damaged product. The expiry-life for each comparator is immaterial for the treatment horizon and assumptions. For unit doses, no wastage is included.

For netarsudil-latanoprost, the model assumes the use of a 2.5 ml bottle and a dose of 60.88 drops / 2.13 ml a cycle (every cycle). Accordingly, given the 100% compliance applied in the model, 22% (0.3ml) of each bottle would be wasted before reaching the post-open expiry date (4 weeks) stated in the SmPC.[76] The SmPC also provides an unopened expiry (shelf life) date of 3 years. Although this period is within the time horizon of the model, it is not material given the expected handling and provision of the medication.

Storage for the opened medication as stated in the SmPC, is in the original carton below 25 degrees Celcius.[76] Storage for the unopened medication as stated in the SmPC, is in a refrigerator (2-8 degrees Celsius) in the original carton. These requirements are considered simple and are therefore assumed to be fulfilled by all patients. It is also assumed that patients do not spill or lose any of the solution.

For each comparator, the storage conditions and expiry-life and shelf-life detailed in the SmPC have been considered for a wastage calculation. The wastage calculation is analogous to that applied for netarsudil-latanoprost. See the following:

- Brinzolamide and timolol – expiry is 4 weeks after opening, a shelf life of 2 years, and no special storage conditions.[77]
- Travoprost and Timolol – expiry is 4 weeks after opening, a shelf life of 2 years, and no special storage conditions beyond not storing above 30 degrees Celcius.[78]

- Dorzolamide and timolol – expiry is 4 weeks after opening, a shelf life of 3 years, with no special storage conditions.[79]

- Latanoprost and timolol – expiry is 4 weeks after opening, a shelf life of 3 years, with no special storage conditions beyond not storing above 25 degrees Celsius. Unopened medication to be refrigerated (2 degrees Celsius – 8 degrees Celsius).[80]

- Tafluprost and timolol – expiry is 4 weeks after opening, with special storage conditions beyond not storing above 25 degrees Celsius. Unopened medication to be refrigerated (2 degrees Celsius – 8 degrees Celsius). Product has a shelf life of 3 years.[81] This product is supplied as a unit dose, so wastage is not considered.

- Bimatoprost and timolol – expiry when kept unrefrigerated at 25 degrees Celsius is 28 days, with no further storage conditions for bottled product.[82]

- Brinzolamide and brimonidine – expiry is 4 weeks after opening with no special storage conditions.[21]

- Brimonidine and timolol – expiry is 4 weeks after opening, with no special storage conditions beyond not storing above 25 degrees Celsius.[83]

Table 41 displays the proportion wasted and incurred cost impact for each comparator, using a basic average of all products within each comparator class. The full table and true CEM values are displayed in Appendix C.

The ml to drop conversion for all comparators in the model is 0.05ml, in line with the literature.[84,85] A study of netarsudil-latanoprost demonstrated an average dose of 0.035ml (35.3 µL), over the full usage of 10 bottles across different lots. [86] A low SE was also reported (2.7% to 5.0%). In line with the findings of Aerie Pharmaceuticals 2023[86] on the container closure system, reflecting the alternative administration apparatus and a smaller applied dose in practice, a different drop conversion has been applied (0.035ml/35.3 µL) for netarsudil-latanoprost.

Table 41: Comparator/intervention wastage

	Expiry-life, cycles (sourced from SmPC)	Basic average across all products within class*			
		Proportion wasted per cycle	No wastage: Price per drop (£)	Wastage: Price per drop (£)	Difference (£)
Netarsudil-latanoprost	1	[redacted]	[redacted]	[redacted]	[redacted]
Brinzolamide-timolol	1	0%	0.07	NA	NA
Travoprost-timolol	1	0%	0.18	NA	NA
Dorzolamide-timolol	1	0%	0.13	0.13	0.00
Latanoprost-timolol	1	0%	0.22	NA	NA
Tafluprost-timolol	Unit dose	NA	0.48	NA	NA
Bimatoprost-timolol	1	7%	0.30	NA	NA
Brimonidine-timolol	1	0%	0.19	NA	NA
Brinzolamide-brimonidine	1	0%	0.09	NA	NA

*See Appendix C for full table and true CEM values

B17. Section B.3.5.2, Health state costs, page 124.

Please provide further description of the calculation approach used to derive health state costs in the model. Please provide the following:

A) Please clarify why the baseline resource use (prior to treatment) from the LiGHT trial was included in the calculations for resource use per cycle (post-treatment) in the current model.

B) Please clarify why it was deemed appropriate to assume that the resource use from the LiGHT trial (including baseline and follow-up appointments) was equivalent to a health state with >30% reduction in IOP in the current economic model.

C) Please clarify why there were no inpatient visits included in the model health state costs, despite these being included and reported in the LiGHT trial.

D) Please provide a justification for assuming that the resource use per cycle associated with optometrist visits is equivalent to the resource use per cycle for ophthalmologist appointments. Please note that optician (equivalent to optometrist) resource use data are available from the referenced LiGHT trial publication (Appendix 12, page 100, table 28).

E) Multipliers of 5% and 2.5% are applied to resource use in the IOP <20% and IOP 20% -30% states based on UK expert opinion. Please provide further description of how these multipliers have been estimated. Please clarify how many clinical experts were consulted and whether they provided an indication of uncertainty around their estimates.

F) The economic model, tab “Data store”, cell “H440” indicates that multipliers of 10% and 20% were applied to the <20% and 20-30% reduction in IOP states respectively. This is inconsistent with the multipliers of 2.5% and 5% applied in the model and described on page 124 of the submission document. Please clarify which multipliers are correct.

G) Please comment on any risks of double counting resource use across both adverse event costs and health state costs (i.e., did the LiGHT trial resource use also incorporate resource use associated with adverse events)?

H) Please consider re-calculating all health state costs, using data available from the literature, applied to a revised model structure as described in clarification query B2.

A) This is an error in the model provided at the time of the submission; the baseline value has now been removed from the average calculation in the model. See updated resource use in Table 42.

Table 42: Updated resource use average

Resource	Previous resource use	Updated resource use
GP visits	0.104	0.089
A&E attendance	0.065	0.066

Inpatient appointments: Planned inpatient admission	6.429	5.667
Inpatient appointments: Emergency inpatient admission	6.857	7.167
Outpatient appointments	0.653	0.623
Optician (Optometrist)	NA	0.3995

Abbreviations: NA - Not available

B) The LiGHT trial data represents treated patients over a 36-month duration. Therefore, when applying an average for the full post-baseline duration of the trial, considering that in the study "treated patients met target IOP" the data is considered reflective of treated patients, rather than untreated patients, Accordingly, resource use is applied to the health state tended to by treated patients.

C) The company acknowledges that planned inpatient visits were included and reported in the LiGHT trial. This is reported in Table 28 of the Gazzard *et al*. 2019b publication under the 'Acute hospital services' subheading as 'Planned inpatient admission'. In the footnote of this table, it is detailed that resource use data for acute hospital services exclude ophthalmology. Therefore, the company deemed that these estimates for the inpatient visits are not reflective of ophthalmic treatment.

D) The company acknowledge that the resource use for optometrist should be sourced from the optician resource use values reported in the LiGHT trial; this has been updated in the model accordingly.

Table 43 displays the calculation post-update. Table 44 displays the optometrist resource use pre- and post-update, where the number of visits per cycle has reduced from 0.22 to 0.07.

Table 43: Optometrist resource use calculation post-update

	Visit: Number of months							
	Baseline	**6**	**12**	**18**	**24**	**30**	**36**	**Average**
Post-update: Optometrist	0.898	0.336	0.364	0.397	0.409	0.394	0.497	0.3995

Table 44: Optometrist resource use pre- and post-update

Resource use	Mean number of clinical visits	Number of patients	Timeframe for clinical visits (months)	Number of visits per cycle	Source
Pre-update: Optometrist visit	2907	362	36	0.22	Assumed equal to ophthalmologist appointments
Post-update: Optometrist visit	-	-	6	0.3995/6 = 0.07	Gazzard *et al.* 2019: 3-year resource use average

E) In the absence of resource data for varying IOP levels, an average of the 36-month duration in the LiGHT trial was used to represent treated patients i.e., those in the >30% reduction in IOP health state. In the absence of numerical evidence from the literature, the 2.5% and 5% multiplier values were selected as conservative estimates for the 20%-30% and <20% states, respectively, to reflect increased resource use from those patients who did not observe IOP improvement.

A UK clinician supported the current model methodology, validating the expected increase in resource use where IOP reduction is insufficient.[87] The clinician citied variation across patients and the numerous possible responses to a lack of patient progress (e.g., adding comparators, SLT, trabeculotomy, phacoemulsification, microinvasive glaucoma surgery) as barriers to identifying exact numerical multipliers. Additional comparators, SLT, and trabeculectomy are controlled for within the model, whilst the minor surgeries (phacoemulsification, microinvasive glaucoma surgery) are considered out of scope of the current submission.

To explore the uncertainty surrounding the estimated multipliers, scenario analyses have been included, varying the rates to the following:

- 3.5% and 5% (to reflect non-linearity of health state definitions)
- 5% & 10% (double original values)
- 10% and 15% (higher values and reflects non-linearity of health state definitions)

The results of the scenario analyses are displayed in

Table ***145*** of Appendix D. Variation from the base case, driven by cost fluctuations, is observed for the ICERs in the scenarios. In all three scenarios, travoprost-timolol moves from being dominated to a positive ICER and brimonidine-timolol shifts from dominating netarsudil-latanoprost to a positive ICER. This reflects both an improvement and worsening with netarsudil-latanoprost relative to the comparators.

F) The correct multipliers are 2.5% and 5%, respectively. The incorrect reference in the model has been corrected; note this was an error in labelling only and has no impact on results.

G) Health state costs were sourced from Table 28 of Gazzard 2019a[88] as it was concluded to be the most suitable and detailed source from the original systematic review. The publication's table includes 'all medical contacts', not specifying if this includes adverse event expenditures. The paper does not report resource use for AEs separately or discuss the possible overlap or interaction of adverse events and medical contacts. Gazzard 2019b[57], which reports the AEs from the same trial in Table 6, specified only pulmonary problems, which occurred in 0.7% patients, as incurring hospital admission.

Of the four UK publications identified from the targeted database searches for the cost and resource use studies, three studies were based in multiple countries including the UK (Hommer *et al.* [2008], Holmstrom *et al.* [2006], and Kobelt *et al.* [1999])[40,42,89] and did not separately report cost or resource use values for a UK patient population only. Therefore, it was deemed that updated cost and resource use estimates were not relevant to the cost-effectiveness model.

The remaining UK-based publication, Orme *et al.* (2012), was the only study identified in the updated targeted searches that reported resource use values for a UK patient population.[41] The publication reported estimates for the frequency of scheduled visits, surgery rates, and the number of follow-ups (Table 67 in Appendix A). However, these estimates were reported according to patient risk group (low or high risk of glaucoma progression) and by treatment arm which included monotherapies not relevant to the cost-effectiveness

model. Risk was defined in this study by a patient's visual field and not IOP. Thus, the resource use estimates were not deemed to be an appropriate source for the cost-effectiveness model. Therefore, while there is a risk of double counting, the most appropriate sources have been utilised and hospital admission costs, which account for the largest expenditures, are not as at risk. Furthermore, Gazzard 2019a[88] was the most recent study identified in the SLR and targeted searches that reported resource use in the UK patient population: this publication reports the most recent data, and is therefore more likely to reflect current UK resource use estimates, providing reliable resource use estimates for the cost-effectiveness model.

H) In line with the response to Question B2, based on published literature, clinical guidelines, and clinician input the current model structure and health states are considered to be the most suitable.

B18. Section B.3.10.3 Scenario analyses, page 153.

Please provide the results of an analysis exploring cost-effectiveness results based on transition probabilities derived for the best and worst-seeing eye separately.

A switch has now been added to the model to select between using the transitions based on the 'study eye' or 'fellow eye' data from the MERCURY 3 trial. ; NMA – Network meta-analysis

Table 46 and Table 47 display the transitions for each methodology for netarsudil-latanoprost and bimatoprost-timolol, respectively. The base case reflects the 'study eye' data. Due to the minimal insight, with an artificial reduction of IOP and misrepresented severity of disease, an average approach has not been included.

Table 89 and Table 140 in Appendix D display the cost-effectiveness results using 'study eye' (base case results) and 'fellow eye' (scenario analysis), respectively. Results in the scenario are largely unchanged, with an increase in the ICER of tafluprost-timolol and a minimal change in the ICERs of other comparators.

It should be noted that the comparator NMA mean differences, applied to the 'fellow eye' MERCURY 3 transitions to create 'fellow eye' transitions for the comparators, are those calculated using the 'study eye' transition data in the NMA. Accordingly, it is assumed that the comparative efficacy from MERCURY 3 to the other trials is equal for the 'study eye' and 'fellow eye'. As stated in Question A9, clinician expert opinion specified that baseline IOP was influential on patient IOP reduction. Consequently, when using the 'study eye' or 'fellow eye' from MERCURY 3 for comparison in the NMA, the equivalent data should be sourced from the comparator trials to facilitate a fair comparison.

Original submission

Equivalent data for the studies used in the original ITC were not available; Kozobolis *et al*. (2017) and ODLASER included only one eye from each patient in the study. The eye selection in ODLASER was dictated by the higher baseline IOP ('worst-seeing eye'), whereas Kozobolis *et al.* (2017) did not state the selection method. Accordingly, the comparison was not included as part of the ITC.

Updated submission (post-clarification questions)

Equivalent data for the studies used in the updated NMA were not available. Table 45 displays the availability of 'fellow eye' data for the studies in the updated NMA. Fellow eye data were not available for any of the comparator trials, rendering the NMA analysis infeasible. Accordingly, this scenario was not included in the NMA.

Table 45: Fellow eye data reporting and selection in the NMA studies

Study	Proportion of patients with treatment in both eyes	'Fellow eye' data available?	'Fellow eye' data notes
MERCURY 3[6]	100%	Yes	Study eye and fellow eye data available separately.
MERCURY 1[14]	100%	No	Analysis was based on the worse seeing eye (higher IOP), or right eye if equal IOP in both eyes. Fellow eye data was not reported.
MERCURY 2[15]	100%	No	Analysis was based on the worse seeing eye (higher IOP), or right eye if equal IOP in both eyes. Fellow eye data was not reported.
Kozobolis *et al*. (2017)[5]	0%	Not applicable	Only one eye included in study.
Katz *et al*. (2013)	NR (patients could enter the study with one or two eyes, if both meet inclusion criteria)	No	Analysis was carried out for the study eye, defined as the worse seeing eye (higher IOP), or right eye if equal IOP in both eyes. Fellow eye data was not reported.
Whitson *et al*. (2013)[13]	NR (patients could enter the study with one or two eyes, but treated both)	No	Analysis was carried out for the study eye, defined as the worse seeing eye (higher IOP), or right eye if equal IOP in both eyes. Fellow eye data was not reported.
Rigollet *et al*. (2011)[8]	NR	No	Not reported.
Nixon *et al*. (2009)[10]	100%	Left and right eye data available, not classified as study and fellow eye.	Analysis was based on the worse seeing eye (higher IOP), or a mean of both if equal IOP at baseline. Fellow eye data was not, explicitly, reported.
DuBiner *et al*. (2001)[16]	100%	No	Both eyes included in analysis but results not separated. Fellow eye data not reported individually.

Abbreviations: IOP – Intraocular pressure; IPD –Individual patient data; NMA – Network meta-analysis

Table 46: Netarsudil-latanoprost transition probabilities (% of patients)

		Study eye			Fellow eye		
Cycle	**Health state**	**<20% reduction in IOP**	**20% - 30% reduction in IOP**	**>30% reduction in IOP**	**<20% reduction in IOP**	**20% - 30% reduction in IOP**	**>30% reduction in IOP**
Baseline -> Cycle 1	<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 1 -> Cycle 2	<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 -> Cycle 3	<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – Intraocular pressure

Table 47: Bimatoprost-timolol transition probabilities (% of patients)

		Study eye			Fellow eye		
Cycle	**Health state**	**<20% reduction in IOP**	**20% - 30% reduction in IOP**	**>30% reduction in IOP**	**<20% reduction in IOP**	**20% - 30% reduction in IOP**	**>30% reduction in IOP**
Baseline -> Cycle 1	<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 1 -> Cycle 2	<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2 -> Cycle 3	<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – Intraocular pressure

Section C: Textual clarification and additional points

C1. Document B, Section B.2.6.1, Primary efficacy endpoint, pages 40-41.

The company submission states that there was a "*statistically significant improvement …for the netarsudil-latanoprost arm in 2/9 time points*". However, the data reported in Table 9 seem to imply that the statistically significant improvement favoured bimatoprost-timolol. Please clarify.

A typographical error is present in Document B. Document B page 40-41 should read: "*statistically significant improvement …for the bimatoprost-timolol arm in 2/9 time points*".

C2. Document B, Section, B.2.9.2.4, Table 24, page 79. Please check whether there is a mistake in the first row of Table 24. Should the number of weeks be the same as in Table 26?

Typographical error in Document B, Table 24. The number of weeks in the third column of this table should read 'Week 8, 8, and 8', as stated in Table 26 of Document B.

C3. Document B, Section B.3.9.1, Base case incremental CEA results, page 139. Clinical experts have indicated that brinzolamide-brimonidine is not commonly used in UK clinical practice in this population; it is typically used as a third- or fourth-line treatment for patients who have tolerability issues. The submission states that this is discussed further in section B.3.12; however, further details do not appear to be provided in section B.3.12 or any other section of the submission. Please provide further discussion as indicated in Section B.3.9.1.

Comments around the suitability of brinzolamide-brimonidine were collected in the June 2023 consultation with three UK clinicians, as described in the below excerpts of Document B[90]:

Page 166: "A fifth stage (June 2023) of clinical input involved validation of long-term clinical efficacy and management of AEs.

- To ratify the appropriateness of using the 'Average' extrapolation method for long-term clinical efficacy in the base case.
- The validation of typical management and resource use for treatment of AEs."

To improve clarity, the company should have added the below bullet points to this section of the submission:

- "To ratify the appropriateness of the comparators and treatment pathway applied in the base case, relative to current UK clinical practice.
- To clarify the suitability of the assumptions around the intervention's placement in the treatment paradigm/pathway, and impact on unmet need."

Reports from the clinical expert consultation which had previously not been included in the submission are now included in the reference pack, labelled as "Clinical validation with Clinician #1-3 June 2023". When asked about existing treatments in-use in UK clinical practice, all three clinicians raised the unsuitability of brinzolamide-brimonidine, noting the following[90–92]:

- Brinzolamide-brimonidine is often poorly tolerated by patients, framing it outside the numerous FDC preparations available for lowering IOP. The treatment combination CAI/AA, of which brinzolamide-brimonidine is the only one included in the model, was flagged as often limited by the side effects of the component medications. Hyperaemia was noted as a possible result of brinzolamide-brimonidine use.
- Brinzolamide-brimonidine is suitable predominantly later in the treatment pathway, for use as a CAI/AA if four topical therapies are required in line with the stepwise increase of medications. This occurs following the trialling of a CAI/BB and either a lack of pressure lowering, obstruction of the angle, or complex secondary glaucoma.
- The treatment combination CAI/AA, of which brinzolamide-brimonidine is the only one included in the model, was noted as often limited by the relatively limited efficacy in the longer term once there has been tachyphylaxis with the alpha-2 adrenergic agonists.

C4. Document B, Section B.3.5.2, Table 57, Health state costs and resource use, page 125.

There appears to be a minor discrepancy between the model calculation and the reported value for A&E resource use frequency for the >30% reduction in IOP state. Please check and confirm the correct value.

Typographical error in Document B, Table 57. Rows 4-6 of this table should read as follows, as altered in Table 48 below. Altered values have been highlighted in bold.

Table 48: Corrected data for Document B, Table 57, rows 4-6

A&E attendance	143.74	NHS: Total outpatient attendance #18 Emergency Medicine Service	<20% reduction in IOP	**0.011**	1.65
			20% - 30% reduction in IOP	0.011	1.61
			>30% reduction in IOP	**0.011**	1.57

Abbreviations: A&E – accident and emergency; IOP – intraocular pressure; NHS – National Health Service

C5. Document B, Section B.3.9, Table 63 – 64 & Table 74-84, p.140-164.

The EAG considers the calculation of dominance to be broadly correct. However, the labelling of results tables may be misleading. Please provide the following additional explanation and clarification of table labelling:

A) Please clarify exactly how the results are calculated, including how treatment strategies were ranked for the fully incremental analysis and how dominance was determined. It appears as if calculations update correctly in the model, but an explanation would be useful for more general readers.

B) Table 63, final column would be more clearly interpreted as “ICER (£) vs. Netarsudil-latanoprost”.

C) Based on the calculation formulae in the model, table 64 does not appear to be an incremental analysis vs. “treatment with lowest total costs” as stated in the table heading. Whilst this may be the case for several scenarios where many treatments are dominated, it is misleading and implies that the NICE reference case has not been followed. Instead, a more accurate description would be “fully incremental analysis”, where the results appear to show ICERs calculated vs. the next less costly, non-dominated alternative.

D) Please report net monetary benefits in the tables as this will improve the interpretation of results.

A) While a dynamic table is provided in the model, Results tab cells C10-K19 (where the results are ordered in terms of incremental costs and then incremental QALYs in line with the NICE template [Table 64 of Document B]) the results in Table 63 of Document B are from the static table in the model, where netarsudil-latanoprost is used as the reference treatment. Accordingly, the incremental costs and incremental QALYs in Table 63 are in comparison to netarsudil-latanoprost. Hence, the ICER column considers the incremental costs and incremental QALYs in the situations outlined in Table 49 below.

Please note that QALYs/LYs may appear as 0 in the model at the displayed number of decimal places – as noted in the submission the very small incremental QALYs between treatments create very sensitive ICERs.

Table 49: ICER calculation explanation

	Incremental costs vs. netarsudil-latanoprost	Incremental QALYs vs. netarsudil-latanoprost	ICER vs. netarsudil-latanoprost
Situation 1	[redacted]	[redacted]	[redacted]
Situation 2	[redacted]	[redacted]	[redacted]
Situation 3	[redacted]	[redacted]	[redacted]
Situation 4	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – incremental cost-effectiveness ratio; QALY – quality-adjusted life year

The values in Table 63 of Document B are from a number of calculations in the model, based on 394 cycles (12 cycles per year * 30.44 cycle length):

- For total costs, the cumulative of treatment costs, add-on treatment costs, health state costs and AE costs, for the 394th cycle are totalled and divided by the cohort number.
- For total LYs gained, the cumulative LYs gained from all three health states for the 394th cycle are totalled and divided by the cohort number.

- For total QALYs gained, the cumulative QALYs gained from all three health states for the 394th cycle are totalled and divided by the cohort number.
- For incremental costs, incremental life years gained (LYG) and QALYs, the equivalent netarsudil-latanoprost is misused.
- For the ICER values, as displayed in Table 49, the incremental costs and divided by the incremental QALYs, with varying outputs depending on the signs of the two values.

B) Agreed. Table 63 title columns should align with those outlined in Table 50. Changes are highlighted in bold.

Table 50: Correction to Table 63 of Document B

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) **vs. netarsudil-latanoprost**

Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALY – quality-adjusted life year

Updated in CEM: Results sheet V10 set to ICER (£) vs. netarsudil-latanoprost.

C) Agreed. Table 64 in Document B title should read 'Deterministic base case results (incremental results vs. the next less costly, non-dominated treatment)'

The CEM has also been updated to reflect this change: 'Results' cell C9 now reads "Dynamic fully incremental results (vs. treatment with lowest total costs)".

D) The CEM has been updated to include net monetary benefit: 'Results' cells L10-L19 and W10-W19 added. Updated results are displayed in Table 89 and Table 90 of Appendix D.

C6. Reference Package. Please confirm whether the publication presenting the ODLASER study results (reference 61) has been supplied in the reference pack.

The publication presenting the ODLASER study results (reference 61) is supplied in the reference pack in the two files named 'ISRCT 2018a' and 'ISRCT 2018b'.

Appendix A

Search strategies for targeted database searches

Table 51 and Table 52 present the search strategies for the clinical targeted database searches. The search strategies for the economic targeted database searches are presented in Table 53 to Table 57.

Clinical search strategy

Table 51: Embase (Embase interface) (27/07/23)

Clinical studies search strategy			
Index	**Description**	**Search terms**	**Hits**
1	Population	'glaucoma'/exp OR 'glaucoma' OR 'open angle glaucoma' OR 'ocular hypertension'	125,691
2	Interventions/ comparators	roclanda/de OR roclanda:ab,ti OR 'latanoprost plus netarsudil'/de OR 'latanoprost plus netarsudil':ab,ti	51
3	Interventions/ comparators	bimatoprost/exp OR bimatoprost:ab,ti OR 'lumigan' OR lumigan:ab,ti	2,249
4	Interventions/ comparators	latanoprost/exp OR latanoprost:ab,ti OR 'xalatan' OR xalatan:ab,ti OR 'xelpros' OR xelpros:ab,ti	5,350
5	Interventions/ comparators	tafluprost/exp OR tafluprost:ab,ti OR 'zioptan' OR zioptan:ab,ti	581
6	Interventions/ comparators	'travoprost'/exp OR travoprost:ab,ti OR 'travatan' OR travatan:ab,ti	1,953
7	Interventions/ Comparators	'timolol maleate'/exp OR 'timolol maleate':ab,ti OR 'blocadren' OR blocraden:ab,ti OR 'timol' OR timol:ab,ti	4,177
8	Interventions/ comparators	brinzolamide/exp OR brinzolamide:ab,ti	1,679

9	Interventions/ comparators	dorzolamide/exp OR dorzolamide:ab,ti OR 'trusopt' OR trusopt:ab,ti	3,554
10	Interventions/ comparators	brimonidine/exp OR brimonidine:ab,ti	5,765
11	Interventions/ comparators	'selective laser trabeculoplasty'/exp OR 'selective laser trabeculoplasty':ab,ti OR 'SLT'/exp OR 'SLT':ab,ti	4,552
12	Study types: RCT Filter[93]	('clinical trial'/de OR 'randomized controlled trial'/de OR 'controlled clinical trial'/de OR 'multicenter study'/de OR 'Phase 3 clinical trial'/de OR 'Phase 4 clinical trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'randomi*ed controlled trial*':ti,ab **OR 'randomi*ed clinical trial*':ti,ab** OR rct:ti,ab OR 'random allocation':ti,ab OR 'randomly allocated':ti,ab OR 'allocated randomly':ti,ab OR (allocated NEXT/2 random):ti,ab OR 'single blind*':ti,ab OR 'double blind*':ti,ab OR ((treble OR triple) NEXT/1 blind*):ti,ab OR placebo*:ti,ab OR 'prospective study'/de) NOT ('case study'/de OR 'case report':ti,ab OR 'abstract report'/de OR 'letter'/de OR 'editorial'/de OR 'note'/de)	2,818,765
13	Observation study filter[93]	'clinical trial'/de OR 'case control study' OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR (cohort NEXT/1 (study OR studies)) OR (('case control' NEXT/1 (study OR studies)):ti,ab) OR (('follow	4,628,449

		up' NEXT/1 (study OR studies)):ti,ab) OR ((observational NEXT/1 (study OR studies)):ti,ab) OR ((epidemiologic* NEXT/1 (study OR studies)):ti,ab) OR (('cross sectional' NEXT/1 (study OR studies)):ti,ab)	
14	Combine Intervention/comparator filters	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	20,788
15	Combine filters and restrict to humans	#1 AND #14 AND (#12 OR #13) AND [humans]/lim	3,458
16	Restrict by date (all time up to 2017)	#15 AND [<1966-2016]/py	2,524

Abbreviations: RCT – randomised clinical trial

Table 52: CENTRAL and Cochrane Clinical Answers (Cochrane Library interface) (27/07/23)

Clinical studies search strategy			
Index	**Description**	**Search terms**	**Hits**
1	Terms for population	MeSH descriptor: [glaucoma] explode all trees	3,943
2	Terms for population	[mh “open angle glaucoma”] OR 'open angle glaucoma' **OR [mh “glaucoma”] OR ‘glaucoma' OR [mh “ocular hypertension”] OR ‘ocular hypertension’**	9,744
3	Combine population terms	#1 OR #2	9,744
4	Interventions/ comparators	[mh “roclanda”] OR roclanda:ab,ti OR [mh “latanoprost plus netasudil”] OR ‘latanoprost plus netarsudil’:ab,ti	1
5	Interventions/ comparators	[mh “bimatoprost”] OR bimatoprost:ab,ti OR ‘lumigan’ OR lumigan:ab,ti	504
6	Interventions/ comparators	[mh “latanoprost”] OR latanoprost:ab,ti OR ‘xalatan’ OR xalatan:ab,ti OR ‘xelpros’ OR xelpros:ab,ti	1,258
7	Interventions/ comparators	[mh “tafluprost”] OR tafluprost:ab,ti OR ‘zioptan’ OR zioptan:ab,ti	109
8	Interventions/ comparators	[mh “travoprost”] OR travoprost:ab,ti OR ‘travatan’ OR travatan:ab,ti	475

9	Interventions/ comparators	[mh “timolol maleate”] OR ‘timolol maleate’:ab,ti OR ‘blocadren’ OR blocraden:ab,ti OR ‘timol’ OR timol:ab,ti	1548
10	Interventions/ comparators	[mh “brinzolamide”] OR brinzolamide:ab,ti	220
11	Interventions/ comparators	[mh “dorzolamide”] OR dorzolamide:ab,ti OR ‘trusopt’ OR trusopt:ab,ti	597
12	Interventions/ comparators	[mh “brimonidine”] OR brimonidine:ab,ti	743
13	Interventions/ comparators	[mh “selective laser trabeculoplasty”] OR ‘selective laser trabeculoplasty’:ab,ti OR [mh “SLT”] OR ‘SLT’:ab,ti	536
14	Combine terms	#4 OR #5 OR #6 OR #7 OR #8 #9 #10 OR #11 #12 OR #13	2,210
15	Limit by date (all time up to 2017)	#14 [with Cochrane Library publication date from Jan 1966 to Dec 2016]	1,111
22	Combine terms (all time up to 2017)	#3 and #15 in trials	880

Economic search strategy

Table 53: Embase (Embase interface) (02/08/23)

Cost-effectiveness, HRQoL and cost and resource use studies search strategy			
Index	**Description**	**Search terms**	**Hits**
1	Population	'glaucoma'/exp OR 'glaucoma' OR 'open angle glaucoma' OR 'ocular hypertension'	125,809
2	Interventions/ comparators	roclanda/de OR roclanda:ab,ti OR ‘latanoprost plus netarsudil’/de OR ‘latanoprost plus netarsudil’:ab,ti	51
3	Interventions/ comparators	bimatoprost/exp OR bimatoprost:ab,ti OR ‘lumigan’ OR lumigan:ab,ti	2,252
4	Interventions/ comparators	latanoprost/exp OR latanoprost:ab,ti OR ‘xalatan’ OR xalatan:ab,ti	5,360

		OR 'xelpros' OR xelpros:ab,ti	
5	Interventions/ comparators	tafluprost/exp OR tafluprost:ab,ti OR 'zioptan' OR zioptan:ab,ti	582
6	Interventions/ comparators	'travoprost'/exp OR travoprost:ab,ti OR 'travatan' OR travatan:ab,ti	1,955
7	Interventions/ Comparators	'timolol maleate'/exp OR 'timolol maleate':ab,ti OR 'blocadren' OR blocraden:ab,ti OR 'timol' OR timol:ab,ti	4,178
8	Interventions/ comparators	brinzolamide/exp OR brinzolamide:ab,ti	1,684
9	Interventions/ comparators	dorzolamide/exp OR dorzolamide:ab,ti OR 'trusopt' OR trusopt:ab,ti	3,559
10	Interventions/ comparators	brimonidine/exp OR brimonidine:ab,ti	5,775
11	Interventions/ comparators	'selective laser trabeculoplasty'/exp OR 'selective laser trabeculoplasty':ab,ti OR 'SLT'/exp OR 'SLT':ab,ti	4,562
12	Combine Intervention/comparator filters	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	20,815
13	Economic Filter[93]	'socioeconomics'/de OR 'cost benefit analysis'/de OR 'cost effectiveness analysis'/de OR 'cost of illness'/de OR 'economic evaluation'/de OR 'cost utility analysis'/de OR 'cost control'/de OR 'economic aspect'/de OR 'financial management'/de OR 'health care cost'/de OR 'health care financing'/de OR 'health economics'/de OR 'hospital cost'/de OR fiscal:ab,ti OR financial:ab,ti OR finance:ab,ti OR funding:ab,ti OR 'cost minimization analysis'/de OR (cost NEXT/1 estimate*) OR (cost NEXT/1 variable*) OR (unit NEXT/1 cost*) OR resource*:ti OR ((resource*	1,225,064

		NEXT/4 (use* OR usage OR utilit*)):ab,ti)	
14	Quality of life filter[94] (https://abstracts.cochrane.org/2015-vienna/sensitivity-search-filter-designed-identify-studies-reporting-health-state-utility)	'quality adjusted life year'/de OR (qaly* OR qald* OR qale* OR qtime*):ab,ti OR (quality adjusted OR adjusted life year*):ab,ti OR 'disability adjusted life':ab,ti OR daly*:ab,ti OR ((index NEXT/3 wellbeing) OR (quality NEXT/3 wellbeing) OR qwb):ab,ti OR (utility NEXT/3 (score* OR scoring OR valu* OR measur* OR evaluat* OR scale* OR instrument* OR weight OR weights OR weighting OR information OR data OR unit OR units OR health* OR life OR estimate* OR elicit* OR disease* OR mean OR cost* OR expenditure* OR gain OR gains OR loss OR losses OR lost OR analysis OR index* OR indices OR overall OR reported OR calculate* OR range* OR increment* OR state OR states OR status)):ab,ti OR utility:ab,ti OR utilities:ab,ti OR disutili*:ab,ti OR (HSUV OR HSUVs):ab,ti OR 'health* year* equivalent*':ab,ti OR (hye OR hyes):ab,ti OR (hui OR hui1 OR hui2 OR hui3):ab,ti OR ('illness state*' OR health state*):ab,ti OR ('euro qual' OR 'euro qual5d' OR 'euro qol5d' OR eq-5d OR eq5-d OR eq5d OR euroqual OR euroqol OR euroqual5d OR euroqol5d):ab,ti OR (eq-sdq OR eqsdq):ab,ti OR (short form* OR shortform*):ab,ti OR (sf36* OR 'sf 36*' OR 'sf thirtysix' OR 'sf thirty six'):ab,ti OR (sf6 OR 'sf 6' OR sf6d OR 'sf 6d' OR 'sf six' OR sfsix OR sf8 OR 'sf 8' OR 'sf eight' OR sfeight):ab,ti OR (sf12 OR 'sf 12' OR 'sf twelve' OR sftwelve):ab,ti OR (sf16 OR	1,079,769

		'sf 16' OR 'sf sixteen' OR sfsixteen):ab,ti OR (sf20 OR 'sf 20' OR 'sf twenty' OR sftwenty):ab,ti OR (15D OR 15-D OR '15 dimension'):ab,ti OR ('standard gamble*' OR sg):ab,ti OR ('time trade off*' OR 'time tradeoff*' OR tto OR timetradeoff*):ab,ti	
15	Combine filters and restrict to humans	#1 AND #12 AND (#13 OR #14) AND [humans]/lim	510
16	Restrict by date (all time up to 2017)	#15 AND [<1966-2016]/py	340

Abbreviations: HRQoL – health-related quality of life

Table 54: NHS EED and HTA search strategy (via University of York website) (02/08/23)

Cost-effectiveness, HRQoL and cost and resource use studies search strategy			
Index	**Description**	**Search terms**	**Hits**
1	Terms for population	MeSH DESCRIPTOR glaucoma EXPLODE ALL TREES in NHS EED, HTA	99
2	Terms for population	**MeSH DESCRIPTOR ocular hypertension EXPLODE ALL TREES IN NHSEED, HTA**	103
3	Combine filters	#1 OR #2	103
4	Economic filter	economics OR cost OR burden OR econ* OR health care cost OR indirect cost OR productivity in NHS EED, HTA	21,739
5	Combine filters	#3 AND #4 in NHS EED, HTA	69
6	QoL filter	qol OR quality of life OR patient satisfaction OR utility OR patient reported outcome OR time tradeoff OR TTO OR activities of daily living OR ADL OR social impact in NHS EED, HTA	8,171
7	Combine terms	#3 AND #6 in NHS EED, HTA	36
8	Combine economic and QoL filter	#5 OR #7 in NHS EED, HTA	72
9	Limit by date (all time to 2015)	#5 AND #7 in NHS EED, HTA	69

Abbreviations: NHS – national health service; EED – economic evaluation database; HTA – health technology assessment; QoL – quality of life

Table 55: ScHARRHUD search strategy (02/08/23)

HRQoL search strategy			
Index	**Description**	**Search terms**	**Hits**
1	Terms for population	glaucoma **OR ocular hypertension OR open angle glaucoma**	5
2	Limit by date	All time to 2017	5

Abbreviations: HRQoL – health-related quality of life; ScHARRHUD - School of Health and Related Research Health Utilities Database

Table 56: EuroQol database search strategy (02/08/23)

HRQoL search strategy			
Index	**Description**	**Search terms**	**Hits**
1	Terms for population	'glaucoma' **OR 'ocular hypertension' OR 'open angle glaucoma'**	0

Abbreviations: EuroQol – euro-quality of life; HRQoL – health-related quality of life

Table 57: International HTA database search strategy (02/08/23)

Cost-effectiveness, HRQoL and cost and resource use studies search strategy			
Index	**Description**	**Search terms**	**Hits**
1	Terms for population	"ocular hypertension" [mhe]	70
2	Terms for population	"glaucoma" [mhe]	68
3	Terms for population	"glaucoma, open-angle" [mhe]	31
4	Combine filters	#1 OR #2 OR #3	70
5	Economic filter	economics OR cost OR burden OR econ* OR health care cost OR indirect cost OR productivity	14,904
6	Combine filters	#4 AND #5	44
7	QoL filter	qol OR quality of life OR patient satisfaction OR utility OR patient reported outcome OR time tradeoff OR TTO OR activities of daily living OR ADL OR social impact	10,606
8	Combine filters	#4 AND #7	31

9	Combine economic and QoL filter	#6 OR #8	49
10	Limit by date	2015 - 2022	19

Abbreviations: HRQoL – health-related quality of life; HTA – health technology assessment; QoL- quality of life

Summary of clinical publications

Table 58: Clinical references identified from the targeted searches (n=7)

Author	Year	Full reference
FDC studies		
Sall *et al*.[11]	2003	Sall KN, Greff LJ, Johnson-Pratt LR, DeLucca PT, Polis AB, Kolodny AH, Fletcher CA, Cassel DA, Boyle DR, Skobieranda F. Dorzolamide/timolol combination versus concomitant administration of brimonidine and timolol: six-month comparison of efficacy and tolerability. Ophthalmology. 2003 Mar 1;110(3):615-24.
Martinez-de-la-Casa *et al*.[9]	2004	Martinez-de-la-Casa JM, Castillo A, Garcia-Feijoo J, Mendez-Hernandez C, Fernandez-Vidal A, Garcia-Sanchez J. Concomitant administration of travoprost and brinzolamide versus fixed latanoprost/timolol combined therapy: three-month comparison of efficacy and safety. Current medical research and opinion. 2004 Sep 1;20(9):1333-9.
Nixon *et al*.[10]	2009	Nixon DR, Yan DB, Chartrand JP, Piemontesi RL, Simonyi S, Hollander DA. Three-month, randomized, parallel-group comparison of brimonidine–timolol versus dorzolamide–timolol fixed-combination therapy. Current medical research and opinion. 2009 Jul 1;25(7):1645-53.
Rigollet *et al*.[8]	2011	Kelly Rigollet JP, Ondategui JA, Pasto A, Lop L. Randomized trial comparing three fixed combinations of prostaglandins/prostamide with timolol maleate. Clinical Ophthalmology. 2011 Feb 10:187-91.
Katz *et al*.[12]	2013	Katz G, DuBiner H, Samples J, Vold S, Sall K. Three-month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2%. JAMA ophthalmology. 2013 Jun 1;131(6):724-30.
Whitson *et al*.[13]	2013	Whitson JT, Realini T, Nguyen QH, McMenemy MG, Goode SM. Six-month results from a Phase III randomized trial of fixed-combination brinzolamide 1%+ brimonidine 0.2% versus brinzolamide or brimonidine monotherapy in glaucoma or ocular hypertension. Clinical Ophthalmology. 2013 Jun 6:1053-60.
Monotherapy studies		
DuBiner *et al*.[16]	2001	DuBiner HB, Mroz M, Shapiro AM, Dirks MS. A comparison of the efficacy and tolerability of brimonidine and latanoprost in adults with open-angle glaucoma or ocular hypertension: a three-month, multicenter, randomized, double-masked, parallel-group trial. Clinical therapeutics. 2001 Dec 1;23(12):1969-83.

Abbreviations: FDC – Fixed-dose combination

Summary of cost-effectiveness publications

Table 59: Summary of UK cost-effectiveness publications identified from the targeted searches (n=5)

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
Kobelt *et al*. 1999[40]	UK (£) and France (French Francs) Cost year: 1997	Societal	Patients with newly diagnosed POAG or OHT that were initially treated with beta-blocker monotherapy Interventions: • Timolol • Timolol and pilocarpine • Dorzolamide • Latanoprost • Laser surgery • Trabeculectomy • Standard treatment	2 years	• The average cost per patient over 12 months for the standard therapy is FF2,389 (US $398) in France and £380 (US $627) in the United Kingdom. • Average total costs with all of the new treatments are lower in both countries than with current therapy. Latanoprost has the lowest-cost at FF2,087 (US $348) and £307 (US $507). • Over 1 year ○ Dorzolamide: FF2305; £324 ○ Latanoprost: FF2087; £307 ○ Timolol and pilocarpine: FF2305 ○ Brimonidine: £325
Holmstrom *et al*. 2006[42]	UK (£), Germany (€), Italy (€), Spain (€), France (€) Cost year: 2005	Health care sector payer	Patients with POAG Interventions: • Bimatoprost 0.03% • Latanoprost 0.005% • Timolol 0.5%	1 year	• ≤13 mmHg C/E ○ Timolol to bimatoprost: £2399 (UK), €3494 (Germany), €2417 (Italy), €3835 (Spain), €4616 (France) ○ Timolol to latanoprost: £4259 (UK), €6050 (Germany), €4112 (Italy), €6650 (Spain), €2860 (France) ○ Bimatoprost: £2569 (UK), €3790 (Germany), €2851 (Italy), €4182 (Spain), €5055 (France)

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					○ Latanoprost: £4660 (UK), €6690 (Germany), €4891 (Italy), €7369 (Spain), €3116 (France) • ≤13 mmHg ICER ○ Timolol to latanoprost: Dominated (UK, Germany, Italy, Spain), €355 (France) ○ Bimatoprost: £18541 (UK), €31655 (Germany), €43720 (Italy), €36886 (Spain), Dominated (France) ○ Latanoprost: Dominated (UK, Germany, Italy, Spain), €27270 (France) • ≤14 mmHg C/E ○ Timolol to bimatoprost: £1341 (UK), €1945 (Germany), €1336 (Italy), €2137 (Spain), €2536 (France) ○ Timolol to latanoprost: £2344 (UK), €3319 (Germany), €2441 (Italy), €3651 (Spain), €1591 (France) ○ Bimatoprost: £1403 (UK), €2063 (Germany), €1570 (Italy), €2285 (Spain), €2792 (France) ○ Latanoprost: £2583 (UK), €3697 (Germany), €2727 (Italy), €4084 (Spain), €1700 (France) • ≤14 mmHg ICER

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					○ Timolol to latanoprost: Dominated (UK, Germany, Italy, Spain), €195 (France) ○ Bimatoprost: £2988 (UK), €5112 (DE), €7613 (IT), €6105 (SP), Dominated (France) ○ Latanoprost: Dominated (UK, Germany, Italy, Spain), €4495 (France) • ≤15 mmHg C/E ○ Timolol to bimatoprost: £959 (UK), €1385 (Germany), €944 (Italy), €1522 (Spain), €2282 (France) ○ Timolol to latanoprost: £2114 (UK), €2983 (Germany), €2000 (Italy), €3284 (Spain), €1132 (France) ○ Bimatoprost: £950 (UK), €1393 (Germany), €1077 (Italy), €1549 (Spain), €2501 (France) ○ Latanoprost: £2318 (UK), €3312 (Germany), €2455 (Italy), €3664 (Spain), €1150 (France) • ≤15 mmHg ICER ○ Timolol to latanoprost: Dominated (UK, Germany, Italy, Spain), €102 (France)

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					○ Bimatoprost: £859 (UK), €1476 (Germany), €2495 (Italy), €1838 (Spain), Dominated (France) ○ Latanoprost: Dominated (UK), Germany, Italy, Spain), €1339 (France) • ≤16 mmHg C/E ○ Timolol to bimatoprost: £661 (UK), €948 (Germany), €638 (Italy), €1043 (Spain), €1125 (France) ○ Timolol to latanoprost: £1045 (UK), €1467 (Germany), €972 (Italy), €1617 (Spain), €774 (France) ○ Bimatoprost: £654 (UK), €955 (Germany), €751 (Italy), €1068 (Spain), €1325 (France) ○ Latanoprost: £1236 (UK), €1758 (Germany), €1324 (Italy), €1954 (Spain), €790 (France) • ≤16 mmHg ICER ○ Timolol to latanoprost: Dominated (UK, Germany, Italy, Spain), €101 (France) ○ Bimatoprost: £594 (UK), €1021 (Germany), €1807 (Italy), €1296 (Spain), Dominated (France)

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					○ Latanoprost: Dominated (UK, Germany, Italy, Spain), €944 (France) • ≤17 mmHg C/E ○ Timolol to bimatoprost: £519 (UK), €743 (Germany), €493 (Italy), €820 (Spain), €784 (France) ○ Timolol to latanoprost: £725 (UK), €1018 (Germany), €665 (Italy), €1125 (Spain), €606 (France) ○ Bimatoprost: £518 (UK), €754 (Germany), €602 (Italy), €847 (Spain), €929 (France) ○ Latanoprost: £870 (UK), €1234 (Germany), €945 (Italy), €1379 (Spain), €625 (France) • ≤17 mmHg ICER ○ Timolol to latanoprost: Dominated (UK, Germany, Italy, Spain), €97 (France) ○ Bimatoprost: £507 (UK), €834 (Germany), €1412 (Italy), €1046 (Spain), Dominated (France) ○ Latanoprost: Dominated (UK, Germany, Italy, Spain), €769 (France) • ≤18 mmHg C/E

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					○ Timolol to bimatoprost: £453 (UK), €635 (Germany), €411 (Italy), €703 (Spain), €675 (France) ○ Timolol to latanoprost: £633 (UK), €872 (Germany), €557 (Italy), €967 (Spain), €517 (France) ○ Bimatoprost: £422 (UK), €611 (Germany), €495 (Italy), €690 (Spain), €802 (France) ○ Latanoprost: £755 (UK), €1065 (Germany), €823 (Italy), €1193 (Spain), €508 (France) • ≤18 mmHg ICER ○ Timolol to latanoprost: Dominated (UK, Germany, Italy, Spain), €71 (France) ○ Bimatoprost: £305 (UK), €521 (Germany), €809 (Italy), €638 (Spain), Dominated (France) ○ Latanoprost: Dominated (UK, Germany, Italy, Spain), €475 (France)
Wickstrøm *et al*. (2010)[36]	UK (£), Spain (€), Italy (€), France (€), Finland (€), Germany (€), The Netherlands	Healthcare	Patients with OAG. Interventions: • Bimatoprost-timolol fixed-combination (BTFC)	3 months	Cost results: • 3-month health care costs for patients treated with BTFC were lower or comparable to those of LTFC in the 10 studied countries Outcomes results:

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
	(€), Norway (€), Sweden (€) and Denmark (€) Cost year: NR		• Latanoprost-timolol fixed-combination (LTFC)		• Significantly more BTFC patients experienced >15% and >20% reduction in IOP compared to LTFC (p=0.003, p<0.001) Cost-effectiveness results: • BTFC was a dominating treatment strategy in all countries. • BTFC was less costly and more effective than LTFC in 8 out of the 10 studied countries (Spain, Italy, Germany, UK, The Netherlands, Norway, Sweden, and Denmark). • BTFC was more effective at equal health care costs in France and Finland.

Orme *et al*. 2012[41]	UK (£)
	Cost year: 2008/09
		NHS	Patients with mild to moderate glaucoma (POAG) or OHT (no visual field loss) in the UK
			Interventions:
			• Latanoprost first line
			• Bimatoprost first line
			• Travoprost first line
				10 years	*Clinical results:*
					Clinical results from the POAG model by treatment strategy: Average cumulative results per patient
					• Latanoprost first line
					  ○ Time stable on treatment:
					  • % of follow-ups where patient stable on medical therapy: 67.29%
					• Time on treatment (months):
					  • Time on first line: 25.91
					  • Time to failure of third line: 63.95
					  • Time before first progression: 56.44
					Time by vision status (mo):
					  • Moderate glaucoma: 43.47

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					• Severe glaucoma: 10.87 Quality of life (QALYs): 5.87 Bimatoprost first line: Time stable on treatment: • % of follow-ups where patient stable on medical therapy: 57.74% Time on treatment (months): • Time on first line: 18.65 • Time to failure of third line: 49.81 • Time before first progression: 44.66 Time by vision status (mo): • Moderate glaucoma: 44.71 • Severe glaucoma: 11.73 Quality of life (QALYs): 5.85 Travoprost first line: Time stable on treatment: • % of follow-ups where patient stable on medical therapy: 56.34% Time on treatment (months): • Time on first line: 20.06 • Time to failure of third line: 48.63 • Time before first progression: 43.63 Time by vision status (mo): • Moderate glaucoma: 44.71

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					• Severe glaucoma: 11.80 • Quality of life (QALYs): 5.85 *Cost results:* Monthly treatment acquisition cost by treatment line 1. First line Latanoprost: £12.48 Bimatoprost: £10.30 Travoprost: £10.17 2. Second line If poor tolerance – timolol: £1.99 If poor IOP control – latanoprost and timolol: £14.32 If poor IOP control – bimatoprost and timolol: £13.95 If poor IOP control – travoprost and timolol: £12.79 3. Third line If poor tolerance – dorzolamide and timolol: £10.05 If poor IOP control – latanoprost, dorzolamide and timolol: £20.65 If poor IOP control – bimatoprost, dorzolamide and timolol: £20.28

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					If poor IOP control – Travoprost, dorzolamide and timolol: £19.12 Resource use unit costs Outpatient visit (first follow-up): £93/visit Outpatient visit (subsequent follow-up): £87/visit Additional consultancy time for treatment switch: • Additional consultant time: £175/hour, £58/visit • Additional nurse time: £40/hour, £13/visit • Additional optometrist time: £40.50/hour, £14/visit • Total excess visit costs: £85/visit Surgery • Trabeculectomy: £996/procedure and /patient • Additional outpatient visits pre/post-surgery: £435/patient Annual cost of low vision • Non-treatment related cost of glaucoma: £725/patient • Care of blind/partially sighted patient: £8,538/patient

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					Economic results from the POAG model by treatment strategy – average cumulative results per patient 1. Latanoprost first line Medical therapy costs: • First line: £303.13 • Second line: £246.86 • Third line: £227.17 • Subtotal cost of medical therapy (all lines): £777.16 Follow-up: • Scheduled follow-up visits: £598.50 • Additional follow-up visits: £190.38 Other costs: • Surgery: £112.04 • Long-term cost of low vision: £4,407.49 • Total cost: £6,086.40 2. Bimatoprost first line Medical therapy costs: • First line: £183.11 • Second line: £93.66 • Third line: £208.60 • Subtotal cost of medical therapy (all lines): £485.36 Follow-up: • Scheduled follow-up visits: £547.46

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					• Additional follow-up visits: £236.14 Other costs: • Surgery: £190.68 • Long-term cost of low vision: £4,699.55 • Total cost: £6,160.04 3. Travoprost first line Medical therapy costs: • First line: £193.73 • Second line: £86.52 • Third line: £207.72 • Subtotal cost of medical therapy (all lines): £487.98 Follow-up: • Scheduled follow-up visits: £552.81 • Additional follow-up visits: £247.45 Other costs: • Surgery: £198.95 • Long-term cost of low vision: £4,723.63 • Total cost: £6,211.70 Analysis of costs and follow-ups over time 1. Latanoprost first line Cost per day of medical treatment: £0.82 Costs in first year: £520.36 Costs in second year: £489.00

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					2. Bimatoprost first line Cost per day of medical treatment: £0.85 Costs in first year: £525.48 Costs in second year: £479.71 3. Travoprost first line Cost per day of medical treatment: £0.88 Costs in first year: £543.56 Costs in second year: £488.49
Hirst *et al*. 2013[39]	UK (£) Cost year: NR	NHS	Patients with POAG Interventions: • Bimatoprost 0.03%/ timolol 0.05% preservative-free FDC • Dorzolamide/timolol preservative-free FDC • Tafluprost/timolol preservative-free non-fixed-combination	Lifetime	Treatment with bimatoprost/timolol dominates dorzolamide/timolol and tafluprost/timolol: Incremental gain of 0.03 QALYs Lifetime costs • Bimatoprost/timolol versus dorzolamide/timolol: £2294 • Bimatoprost/timolol versus tafluprost/timolol: £2919 BTFC PF dominates DTFC PF and TTUF PF

Abbreviations: BTFC - Bimatoprost-timolol fixed-combination C/E – Cost-effectiveness; FDC – Fixed-dose combination; ICER – incremental cost-effectiveness ratio; LTFC – Latanoprost-timolol fixed-combination; NHS – National Health Service; NR – Not reported; OHT – Ocular hypertension; POAG – Primary open-angle glaucoma; QALY – Quality adjusted life year; UK – United Kingdom

Table 60: Summary of non-UK cost-effectiveness publications identified from the targeted searches (n=13)

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
Cottle *et al*. 1988[45]	Canada ($) Cost year: NR	NR	Patients with newly diagnosed and untreated POAG • Pilocarpine 0.5% • Pilocarpine 1.0% • Pilocarpine 2.0% • Timolol 0.25% • Timolol 0.5%	1 year	Number of patients whose condition was controlled with mild or no adverse reactions against the number of patients who started on the treatment • Pilocarpine 2.0%: 0.36 • Pilocarpine 1.0%: 0.54 • Timoptic 0.25%: 0.39 • Timoptic 0.5%: 0.50 • Propine 0.1%: 0.60 Cost-effectiveness • Pilocarpine 2.0%: 2.08 • Pilocarpine 1.0%: 3.08 • Timolol 0.25%: 8.89 • Timolol 0.5%: 8.28 • Dipivifrin 0.1%: 4.08
Rocchi *et al*. 1997[49]	Canada ($) Cost year: 1996	Provincial ministry of health	Patients with POAG aged over 65 years Interventions: • Dorzolamide • Pilocarpine	10 years	• Dorzolamide had a QALY gain of 0.118 QALYs per patient over 10 years over pilocarpine. • An additional $1,107.96/patient over 10 years for dorzolamide over pilocarpine

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					• ICER for dorzolamide versus pilocarpine: $9490
Marchetti *et al*. 2001	US ($) Cost year: NR	NR	Patients with newly diagnosed or currently untreated OHT or OAG Interventions: • Brimonidine 0.2% • Betaxolol 0.25%	1 year	Clinical success rates of therapy • Brimonidine: 73.9% • Betaxolol: 56.2% Cost-effectiveness ratio • Brimonidine: $407.81 ($301/0.74) • Betaxolol: $583.97 ($328/0.56)
Bernard *et al*. 2003[43]	France (€) Cost year: 2002	Third-party payer	Patients with OAG or OHT Interventions: • Beta-blocker first line • Latanoprost first line	2 years, 3 years	Days of IOP control over a 2-year period (Mean [SD]) • Beta-blocker first line: 653.35 (99.15) • Latanoprost first line: 702.98 (65.83) Days of IOP control over a 3-year period (Mean [SD]) • Beta-blocker first line: 973.27 (168) • Latanoprost first line: 1046.97 (112.39) Mean costs over a 2-year period • Beta-blocker first line: €539.46 • Latanoprost first line: €580.38 Mean costs over a 3-year period

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					• Beta-blocker first line: €817.43 • Latanoprost first line: €844.02 Incremental cost over a 2-year period • Beta-blocker first line: - • Latanoprost first line: €40.92 Incremental cost over a 3-year period • Beta-blocker first line: - • Latanoprost first line: €26.59 Incremental days of IOP control over a 2-year period • Beta-blocker first line: - • Latanoprost first line: 49.67 Incremental days of IOP control over a 3-year period • Beta-blocker first line: - • Latanoprost first line: 73.74 Cost per IOP-controlled day gained over a 2-year period • Beta-blocker first line: - • Latanoprost first line: €0.82 Cost per IOP-controlled day gained over a 3-year period

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					• Beta-blocker first line: - • Latanoprost first line: €0.36
Rouland *et al*. 2003[50]	France, Italy, Portugal and Spain (€) Cost year: 2000	Payer (including the part paid by third party payers plus out-of-pocket expenses)	Patients with OHT and/or POAG who had not responded to or could not tolerate beta-blocker therapy Interventions: • Brinzolamide (b.i.d. or t.i.d) • Dorzolamide (b.i.d. or t.i.d)	3 months	Cost per treatment of timolol • France: €7.02 • Italy: €5.44 • Portugal: €5.99 • Spain: €3.43 Cost per treatment of latanoprost: • France: €20.98 • Italy: €24.53 • Portugal: €23.19 • Spain: €23.64 Cost per treatment of dorzolamide: • France: €14.08 • Italy: €14.51 • Portugal: €13.73 • Spain: €13.25 Cost per treatment of brinzolamide: • France: €14.74 • Italy: €14.98 • Portugal: €13.73 (hypothetical price)

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					• Spain: €13.91 Daily cost of each CAI regimen – brinzolamide b.i.d monotherapy • France: €0.53 • Italy: €0.54 • Portugal: €0.49 • Spain: €0.50 Daily cost of each CAI regimen – brinzolamide t.i.d monotherapy • France: €0.57 • Italy: €0.58 • Portugal: €0.53 • Spain: €0.54 Daily cost of each CAI regimen – dorzolamide t.i.d monotherapy • France: €0.67 • Italy: €0.69 • Portugal: €0.71 • Spain: €0.63 Daily cost of each CAI regimen – dorzolamide b.i.d monotherapy • France: €0.50

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					• Italy: €0.52 • Portugal: €0.53 • Spain: €0.47 Breakeven price • France: €14.72 • Italy: € 15.43 • Portugal: € 15.81 • Spain: € 15.21 Average savings per patient • France: -€0.03 • Italy: €1.17 • Portugal: €2.03 • Spain: €3.05
Kymes *et al*. 2006[46]	US ($) Cost year: 2005	Societal	Patients with IOP ≥24 mm Hg Interventions: • Treat no one with IOP ≥24 mmHg until they developed POAG • Treat only patients with IOP ≥ 24 mmHg and an annual risk of the	Lifetime	Total QALYs • Treat no one: 13.54 • Treat ≥5%: 13.56 • Treat ≥2%: 13.59 • Treat everyone: 13.59 Total costs: • Treat no one with IOP ≥24 mm Hg until they developed POAG (“Treat no one”)- $4006

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
			development of POAG of ≥5% • Treat only patients with IOP ≥24 mmHg and an annual risk of the development of POAG of ≥2% • Treat everyone with IOP of ≥24 mmHg		• Treat only persons with IOP of ≥24 mm Hg and an annual risk of the development of POAG of ≥5% (“Treat≥5%”)- $4086 • Treat only persons with IOP of ≥24 mm Hg and an annual risk of the development of POAG of ≥2% (“Treat ≥2%”)-$5308 • Treat everyone with IOP of ≥ 24 mm Hg (“Treat everyone”)- $11245 ICER • Treat ≥5% versus treat no one: $3670/QALY • Treat ≥5% versus treat ≥2%: $42,430/QALY • Treat all versus treat ≥2%: Dominated
Stewart *et al*. 2008[52]	US ($) Cost year: NR	NR	Patients with OHT Interventions: • OHT treatment (treatment not specified – average of latanoprost, bimatoprost, travoprost, generic timolol, and brimonidine) • No treatment	5 years	QALYs over 5 years • No treatment arm: 4.45 • Treatment arm: 4.48 Cost/efficacy over 5 years • No treatment arm: $554 • Treatment arm: $1116 Baseline ICER: $89,072 Risk factor analyses ICERs • Age (plus one decade): $62,756 • Age (plus two decades): $45,155

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					• IOP (plus 1 mmHg): $75,676 • IOP (plus 2 mmHg): $63,696 • IOP (plus 3 mmHg): $54,755 • IOP (plus 4 mmHg): $46,748 • IOP (plus 5 mmHg): $40,157 • Cup-to-disc ratio (plus 0.5): $55,431 • Cup-to-disc ratio (plus 0.6): $35,633 • Cup-to-disc ratio (plus 0.7): $23,061 • Cup-to-disc ratio (plus 0.8): $14,677 • Corneal thickness (plus 40 µm): $36,683 • Corneal thickness (plus 80 µm): $15,567
Kymes *et al*. 2010[47]	US ($) Cost year: NR	Societal	Patients with OHT aged 45, 55 or 65 years of age at baseline Interventions: • SoC • No treatment	Lifetime	Life expectancy needed to be cost-effective conditional on age when starting treatment and the percentage treated at a WTP of $50,000 • Age 45 - Treat 2%: 21 years • Age 45 - Treat 3%: 15 years • Age 45 - Treat 4%: 11 years • Age 45 - Treat 5%: 9 years • Age 55 - Treat 2%: 24 years • Age 55 - Treat 3%: 19 years • Age 55 - Treat 4%: 18 years • Age 55 - Treat 5%: 10 years • Age 65 - Treat 2%: 26 years • Age 65 - Treat 3%: 25 years

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					• Age 65 - Treat 4%: 23 years • Age 65 - Treat 5%: 21 years Life expectancy needed to be cost-effective conditional on age when starting treatment and the percentage treated at a WTP of $75,000 • Age 45 - Treat 2%: 18 years • Age 45 - Treat 3%: 14 years • Age 45 - Treat 4%: 9 years • Age 45 - Treat 5%: 7 years • Age 55 - Treat 2%: 21 years • Age 55 - Treat 3%: 17 years • Age 55 - Treat 4%: 16 years • Age 55 - Treat 5%: 8 years • Age 65 - Treat 2%: 23 years • Age 65 - Treat 3%: 22 years • Age 65 - Treat 4%: 21 years • Age 65 - Treat 5%: 19 years Life expectancy needed to be cost-effective conditional on age when starting treatment and the percentage treated at a WTP of $100,000 • Age 45 - Treat 2%: 17 years • Age 45 - Treat 3%: 13 years • Age 45 - Treat 4%: 8 years • Age 45 - Treat 5%: 7 years

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					• Age 55 - Treat 2%: 20 years • Age 55 - Treat 3%: 16 years • Age 55 - Treat 4%: 15 years • Age 55 - Treat 5%: 8 years • Age 65 - Treat 2%: 21 years • Age 65 - Treat 3%: 21 years • Age 65 - Treat 4%: 19 years
Blaser *et al*. 2011[44]	US ($) Cost year: 2010	Managed care organisation	Patients with OAG and OHT Interventions: • Bimatoprost • Latanoprost • Travoprost	1 year	ICER for first-line therapy with a preferred prostaglandin per effectively treated patient • Bimatoprost: $815.13 • Latanoprost: $961.71 • Travoprost: $889.13 ICER for first-line therapy with timolol followed by a preferred prostaglandin per effectively treated patient • Bimatoprost: $436.77 • Latanoprost: $499.77 • Travoprost: $462.21 ICER if preferred prostaglandin not selected • First-line therapy: $910.95 • Second line therapy: $477.77
Peeters *et al*. 2012[37]	The Netherlands (€)	Healthcare	Patients with POAG Interventions:	Lifetime	ICER at a 4% discount

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
	Cost year: 2003		• Timolol • Latanoprost		• Latanoprost: $536,852 • Latanoprost (Initial IOP of 25 mmHg): $547,276 • Latanoprost (Initial IOP of 30 mmHg): $7,068,037 ICER at a 0% discount • Latanoprost: $253,011 • Latanoprost (Initial IOP of 25 mmHg): $254,150 Latanoprost (Initial IOP of 30 mmHg): $2,009,703
Stein *et al*. 2012[51]	US ($) Cost year: 2010	Payer	Patients aged 60 years old with mild OAG Interventions: • PGAs • Laser trabeculoplasty • No treatment	25 years	QALYs gained over 25 years • No treatment: 16.06 • Laser trabeculoplasty: 16.71 • PGAs: 17.14 Base case ICERs • Laser trabeculoplasty versus no treatment: $16,824/QALY • PGAs versus no treatment: $14,179/QALY
van Gestel *et al*. 2012[54]	The Netherlands (€) Cost year: 2006	Societal	Patients with POAG Interventions: • Latanoprost	Lifetime	ICER/QALY • No treatment: Dominated • Latanoprost: €12,931 • Targetting IOP: Dominant

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
			• Tretament targeting IOP of 15 mmHg • Visual field measurements every 6 months • Visual field measurements every 24 months		• Visual field measurements every 6 months: €173,486 • Visual field measurements every 24 months: €21,516
van Gestel *et al*. 2014[53]	The Netherlands (€) Cost year: 2006	Societal	Patients with OHT Interventions: • Direct pressure lowering treatment for OHT (timolol) • 'Watchful waiting' (I.e. either monitor and treat only after conversion to POAG has occurred or treat everyone once OHT has been diagnosed)	Lifetime (mean: 26 years, 10 years	Costs at a 10 year time horizon • 'Watchful waiting': €2302 • Direct treatment: €3415 Costs at a 26 year time horizon • 'Watchful waiting': €18,327 • Direct treatment: €14,343 QALYs at a 10 year time horizon • 'Watchful waiting': 8.15 • Direct treatment: 8.18 QALYs at a 26 year time horizon • 'Watchful waiting': 21.79 • Direct treatment: 22.17 Discounted costs at a 10 year time horizon

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					• 'Watchful waiting': €1891 • Direct treatment: €2844 Discounted costs at a 26 year time horizon • 'Watchful waiting': €7722 • Direct treatment: €7073 Discounted QALYs at a 10 year time horizon • 'Watchful waiting': 7.62 • Direct treatment: 7.65 Discounted QALYs at a 26 year time horizon • 'Watchful waiting': 17.55 • Direct treatment: 17.81 Incremental costs and QALYs at a 10 year time horizon • Costs: €1113 • QALYs: 0.03 • Discounted costs: €957 • Discounted QALYs: 0.03 Incremental costs and QALYs at a 26 year time horizon • Costs: -€3984 • QALYs: 0.38

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					• Discounted costs: -€649 • Discounted QALYs: 0.27 ICER at a 10 year time horizon • Undiscounted: €35,573 • Discounted: €33,645 ICER at a 26 year time horizon • Undiscounted: Dominant • Discounted: Dominant Subgroup analyses of OHT patients based on initial IOP and average 5 year risk of conversion – Low risk (HR=0.5) • 22 mmHg incremental costs: €1,259 • 22 mmHg incremental QALYs: 0.082 • 22 mmHg ICER: €15,425 • 24 mmHg incremental costs: €851 • 24 mmHg incremental QALYs: 0.122 • 24 mmHg ICER: €6,954 • 26 mmHg incremental costs: €624 • 26 mmHg incremental QALYs: 0.175 • 26 mmHg ICER: €3,563 • 28 mmHg incremental costs: €1,127 • 28 mmHg incremental QALYs: 0.221

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					• 28 mmHg ICER: €5,088 • 30 mmHg incremental costs: €807 • 30 mmHg incremental QALYs: 0.303 • 30 mmHg ICER: €2,660 • 32 mmHg incremental costs: €49 • 32 mmHg incremental QALYs: 0.403 • 32 mmHg ICER: €121 Neutral risk (HR=1.0) • 22 mmHg incremental costs: €541 • 22 mmHg incremental QALYs: 0.149 • 22 mmHg ICER: €3,629 • 24 mmHg incremental costs: -€193 • 24 mmHg incremental QALYs: 0.214 • 24 mmHg ICER: Dominant • 26 mmHg incremental costs: -€765 • 26 mmHg incremental QALYs: 0.293 • 26 mmHg ICER: Dominant • 28 mmHg incremental costs: -€1,085 • 28 mmHg incremental QALYs: 0.374 • 28 mmHg ICER: Dominant • 30 mmHg incremental costs: -€1,788 • 30 mmHg incremental QALYs: 0.469 • 30 mmHg ICER: Dominant • 32 mmHg incremental costs: -€2,826

Reference	Region, currency, (cost year)	Perspective	Population and intervention	Time horizon	Outcomes/results
					• 32 mmHg incremental QALYs: 0.571 • 32 mmHg ICER: Dominant High risk (HR=2.0) • 24 mmHg ICER: Dominant • 26 mmHg incremental costs: -€1,995 • 26 mmHg incremental QALYs: 0.370 • 26 mmHg ICER: Dominant • 28 mmHg incremental costs: -€3,168 • 28 mmHg incremental QALYs: 0.497 • 28 mmHg ICER: Dominant • 30 mmHg incremental costs: -€4,405 • 30 mmHg incremental QALYs: 0.583 • 30 mmHg ICER: Dominant • 32 mmHg incremental costs: -€6,046 • 32 mmHg incremental QALYs: 0.728 • 32 mmHg ICER: Dominant

Abbreviations: bid – Two times a day; CAI – Carbonic anhydrase inhibitor; C/E – Cost-effectiveness; FDC – Fixed-dose combination; HR – Hazard ratio; ICER – Incremental cost-effectiveness ratio; NR – Not reported; OAG – Open-angle glaucoma; OHT – Ocular hypertension; PGA – Prostaglandin analogue; POAG – Primary open-angle glaucoma; QALY – Quality adjusted life year; SD – Standard deviation; SoC – Standard of care; tid – Three times a day; US – United States; WTP – Willingness-to-pay

Table 61: Quality assessment of UK cost-effectiveness studies identified from the targeted searches (n=5)

Study question	Study name				
	Kobelt *et al.* 1999[40]	Holmstrom *et al.* 2006[42]	Wickstrøm *et al.* 2010[36]	Orme *et al.* 2012[41]	Hirst *et al.* 2013[39]
1. Was the research question stated?	Yes	Yes	Yes	Yes	Yes
2. Was the economic importance of the research question stated?	Yes	Yes	No	Yes	No
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	Yes	Yes	Yes	Yes
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	Yes	Yes	No	No
5. Were the alternatives being compared clearly described?	No	Yes	Yes	Yes	Yes
6. Was the form of economic evaluation stated?	No	Yes	Yes	No	Yes
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Yes	No	Yes	Yes
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Yes	No	Yes	Yes
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	No	No	N/A	N/A
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	N/A	N/A	Yes	No
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	No	Yes	No	No	Yes
12. Were the methods used to value health states and other benefits stated?	No	Yes	No	Yes	No
13. Were the details of the subjects from whom valuations were obtained given?	No	Yes	No	No	No
14. Were productivity changes (if included) reported separately?	N/A	N/A	N/A	N/A	N/A
15. Was the relevance of productivity changes to the study question discussed?	No	No	No	No	No
16. Were quantities of resources reported separately from their unit cost?	No	Yes	No	Yes	No
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Yes	No	Yes	Yes
18. Were currency and price data recorded?	Yes	Yes	No	No	No
19. Were details of price adjustments for inflation or currency conversion given?	No	Yes	No	No	No

Study question	Study name				
	Kobelt *et al.* 1999[40]	Holmstrom *et al.* 2006[42]	Wickstrøm *et al.* 2010[36]	Orme *et al.* 2012[41]	Hirst *et al.* 2013[39]
20. Were details of any model used given?	Yes	Yes	No	Yes	No
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Yes	No	Yes	No
22. Was the time horizon of cost and benefits stated?	Yes	Yes	Yes	Yes	Yes
23. Was the discount rate stated?	No	No	No	Yes	No
24. Was the choice of rate justified?	No	N/A	N/A	Yes	No
25. Was an explanation given if cost or benefits were not discounted?	No	No	N/A	N/A	No
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	No	No	No	No
27. Was the approach to sensitivity analysis described?	Yes	Yes	No	Yes	Yes
28. Was the choice of variables for sensitivity analysis justified?	Yes	No	No	Yes	No
29. Were the ranges over which the parameters were varied stated?	Yes	Yes	No	No	No
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	Yes	Yes	N/A	Yes
31. Was an incremental analysis reported?	No	Yes	Yes	No	Yes
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	Yes	No	No	No
33. Was the answer to the study question given?	Yes	Yes	Yes	Yes	Yes
34. Did conclusions follow from the data reported?	Yes	Yes	Yes	Yes	Yes
35. Were conclusions accompanied by the appropriate caveats?	Yes	Yes	No	Yes	No
36. Were generalisability issues addressed?	Yes	No	No	No	No

Abbreviations: N/A – Not applicable; UK – United Kingdom

Table 62: Quality assessment of non-UK cost-effectiveness studies identified from the targeted searches (n=13) (part A)

Study question	Study name				
	Cottle *et al.* 1988[45]	Rocchi *et al.* 1997[49]	Marchetti *et al.* 2001[48]	Bernard *et al.* 2003[43]	Rouland *et al.* 2003[50]
1. Was the research question stated?	Yes	Yes	Yes	Yes	Yes
2. Was the economic importance of the research question stated?	Yes	Yes	Yes	Yes	Yes
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	Yes	No	Yes	Yes
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Yes	No	Yes	Yes
5. Were the alternatives being compared clearly described?	Yes	No	Yes	Yes	Yes
6. Was the form of economic evaluation stated?	Yes	Yes	Yes	Yes	Yes
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Yes	Yes	Yes	Yes
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Yes	Yes	Yes	Yes
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	No	Yes	N/A	Yes
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	N/A	N/A	No	N/A
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Yes	Yes	Yes	Yes
12. Were the methods used to value health states and other benefits stated?	No	Yes	No	No	N/A
13. Were the details of the subjects from whom valuations were obtained given?	Yes	No	Yes	No	N/A
14. Were productivity changes (if included) reported separately?	N/A	N/A	N/A	N/A	N/A
15. Was the relevance of productivity changes to the study question discussed?	No	No	No	No	No
16. Were quantities of resources reported separately from their unit cost?	No	No	No	Yes	No
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Yes	Yes	Yes	Yes
18. Were currency and price data recorded?	Yes	Yes	Yes	Yes	Yes
19. Were details of price adjustments for inflation or currency conversion given?	No	No	No	No	No

Study question	Study name				
	Cottle *et al.* 1988[45]	Rocchi *et al.* 1997[49]	Marchetti *et al.* 2001[48]	Bernard *et al.* 2003[43]	Rouland *et al.* 2003[50]
20. Were details of any model used given?	No	Yes	Yes	Yes	Yes
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	Yes	Yes	No	Yes
22. Was the time horizon of cost and benefits stated?	No	Yes	Yes	Yes	Yes
23. Was the discount rate stated?	No	Yes	No	Yes	No
24. Was the choice of rate justified?	N/A	No	No	No	No
25. Was an explanation given if cost or benefits were not discounted?	No	N/A	No	N/A	No
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	No	No	Yes	No
27. Was the approach to sensitivity analysis described?	No	Yes	Yes	Yes	Yes
28. Was the choice of variables for sensitivity analysis justified?	N/A	Yes	No	Yes	No
29. Were the ranges over which the parameters were varied stated?	N/A	Yes	No	Yes	No
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	N/A	No	Yes	Yes
31. Was an incremental analysis reported?	No	No	No	Yes	No
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	No	No	No	No
33. Was the answer to the study question given?	Yes	Yes	Yes	Yes	Yes
34. Did conclusions follow from the data reported?	Yes	Yes	Yes	Yes	Yes
35. Were conclusions accompanied by the appropriate caveats?	Yes	Yes	No	Yes	Yes
36. Were generalisability issues addressed?	No	Yes	No	No	No

Abbreviations: N/A – Not applicable; UK – United Kingdom

Table 63: Quality assessment of non-UK cost-effectiveness studies identified from the targeted searches (n=13) (part B)

Study question	Study name				
	Kymes *et al.* 2006[46]	Stewart *et al.* 2008[52]	Kymes *et al.* 2010[47]	Blaser *et al.* 2011[44]	Peeters *et al.* 2012[37]
1. Was the research question stated?	Yes	Yes	Yes	Yes	Yes
2. Was the economic importance of the research question stated?	No	Yes	Yes	No	Yes
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	No	Yes	Yes	Yes
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	No	No	Yes	Yes
5. Were the alternatives being compared clearly described?	Yes	No	No	Yes	Yes
6. Was the form of economic evaluation stated?	Yes	Yes	Yes	No	Yes
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	Yes	No	No	Yes
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Yes	No	No	No
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	No	N/A	No	No
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	N/A	No	No	N/A
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Yes	Yes	No	Yes
12. Were the methods used to value health states and other benefits stated?	Yes	Yes	No	No	No
13. Were the details of the subjects from whom valuations were obtained given?	No	No	No	No	No
14. Were productivity changes (if included) reported separately?	N/A	N/A	N/A	N/A	N/A
15. Was the relevance of productivity changes to the study question discussed?	No	No	No	No	No
16. Were quantities of resources reported separately from their unit cost?	No	No	No	No	No
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Yes	No	Yes	Yes
18. Were currency and price data recorded?	Yes	Yes	Yes	Yes	Yes
19. Were details of price adjustments for inflation or currency conversion given?	No	No	No	No	Yes

Study question	Study name				
	Kymes *et al.* 2006[46]	Stewart *et al.* 2008[52]	Kymes *et al.* 2010[47]	Blaser *et al.* 2011[44]	Peeters *et al.* 2012[37]
20. Were details of any model used given?	Yes	Yes	Yes	Yes	Yes
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	Yes	No	No	Yes
22. Was the time horizon of cost and benefits stated?	Yes	Yes	Yes	No	Yes
23. Was the discount rate stated?	Yes	Yes	Yes	No	Yes
24. Was the choice of rate justified?	Yes	No	No	No	Yes
25. Was an explanation given if cost or benefits were not discounted?	N/A	No	N/A	No	N/A
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	No	No	No	No
27. Was the approach to sensitivity analysis described?	Yes	Yes	Yes	No	Yes
28. Was the choice of variables for sensitivity analysis justified?	No	Yes	No	No	No
29. Were the ranges over which the parameters were varied stated?	Yes	Yes	Yes	No	Yes
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	No	Yes	Yes	Yes
31. Was an incremental analysis reported?	Yes	Yes	No	Yes	No
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	Yes	No	No	Yes
33. Was the answer to the study question given?	Yes	Yes	Yes	Yes	Yes
34. Did conclusions follow from the data reported?	Yes	Yes	Yes	Yes	Yes
35. Were conclusions accompanied by the appropriate caveats?	Yes	Yes	Yes	No	Yes
36. Were generalisability issues addressed?	Yes	No	Yes	No	No

Abbreviations: N/A – not applicable; UK – United Kingdom

Table 64: Quality assessment of non-UK cost-effectiveness studies identified from the targeted searches (n=13) (part C)

Study question	Study name		
	Stein *et al.* 2012[51]	van Gestel *et al.* 2012[54]	van Gestel *et al.* 2014[53]
1. Was the research question stated?	Yes	Yes	Yes
2. Was the economic importance of the research question stated?	Yes	Yes	Yes
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	Yes	Yes
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Yes	Yes
5. Were the alternatives being compared clearly described?	Yes	Yes	No
6. Was the form of economic evaluation stated?	Yes	Yes	No
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	No	No
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Yes	Yes
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	N/A	N/A
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	Yes	N/A
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Yes	Yes
12. Were the methods used to value health states and other benefits stated?	Yes	No	Yes
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Yes	No
14. Were productivity changes (if included) reported separately?	N/A	Yes	No
15. Was the relevance of productivity changes to the study question discussed?	No	No	No
16. Were quantities of resources reported separately from their unit cost?	No	Yes	No
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Yes	Yes
18. Were currency and price data recorded?	Yes	Yes	Yes
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Yes	Yes
20. Were details of any model used given?	Yes	Yes	Yes
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Yes	Yes
22. Was the time horizon of cost and benefits stated?	Yes	Yes	Yes
23. Was the discount rate stated?	Yes	Yes	Yes

Study question	Study name		
	Stein *et al.* 2012[51]	van Gestel *et al.* 2012[54]	van Gestel *et al.* 2014[53]
24. Was the choice of rate justified?	No	No	No
25. Was an explanation given if cost or benefits were not discounted?	No	N/A	N/A
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	Yes	No
27. Was the approach to sensitivity analysis described?	Yes	Yes	Yes
28. Was the choice of variables for sensitivity analysis justified?	Yes	Yes	No
29. Were the ranges over which the parameters were varied stated?	Yes	Yes	No
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Yes	Yes
31. Was an incremental analysis reported?	Yes	Yes	Yes
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Yes	Yes
33. Was the answer to the study question given?	Yes	Yes	Yes
34. Did conclusions follow from the data reported?	Yes	Yes	Yes
35. Were conclusions accompanied by the appropriate caveats?	Yes	Yes	Yes
36. Were generalisability issues addressed?	Yes	No	Yes

Abbreviations: N/A – Not applicable; UK – United Kingdom

Summary of HRQoL publications

Table 65: Summary of HRQoL publications identified from the targeted searches (n=5)

Reference	Sample size	Population	Information on recruitment	Intervention (N)	Response rates	Description of health states	Adverse reactions	Appropriateness of health states given the condition and treatment pathway
Stewart *et al.* (2008)[52]	NR	NR	NR	NR	NR	NR	NR	N/A
Bozzani *et al.* (2012)[95]	132	Patients with POAG in one or both eyes from Moorfields Eye Hospital	Patients had to be at least 18 years old, English-speaking and free from conditions preventing reliable visual testing and interviewing. Exclusion criteria were eye surgery in the preceding 6 weeks and any ocular co-morbidities contributing to loss of vision.	NR	NR	NR	NR	N/A
Orme *et al.* (2012)[41]	NR	NR	NR	Latanoprost first line, bimatoprost first line,	NR	• OHT • Glaucoma: mild	NR	Appropriate

Reference	Sample size	Population	Information on recruitment	Intervention (N)	Response rates	Description of health states	Adverse reactions	Appropriateness of health states given the condition and treatment pathway
				travoprost first line		• Glaucoma: moderate • Glaucoma: severe • Death		
Stein *et al.* (2012)[51]	NR	Patients aged 60 years old with mild OAG	NR	NR	NR	• Mild glaucoma • Moderate glaucoma • Severe glaucoma • Unilateral blindness • Bilateral blindness • Death	NR	Appropriate
van Gestel *et al.* (2014)[53]	654	Medical files of patients with OHT or POAG from seven hospitals in The Netherlands	NR	NR	537/654 (81%)	N/A	NR	N/A

Abbreviations: HRQoL – Health-related quality of life; NR – Not reported; OHT – Ocular hypertension; POAG – Primary open-angle glaucoma; N/A – Not applicable

Table 66. Summary of HRQoL publications identified from the targeted searches (n=5) (cont.)

Reference	Method of elicitation	Method of valuation	Mapping	Uncertainty around values	Utility values with confidence intervals	Consistency with reference case
Stewart *et al.* (2008) [52]	Modified from the published literature, based on different levels of visual acuity	NR	NR	NR	• No visual loss: 0.9 • Mild visual loss: 0.68 • Moderate visual loss: 0.57	Not consistent with reference case, as EQ-5D was not reported by patients
Bozzani *et al.* (2012) [95]	• Utility measures: EQ-5D and SF-36 providing preferences associated with generic health states. Time-Trade-Off (TTO) for patients to state how many more years they expected to live, and to quantify how many of those years (Y) - if any - they	• EQ-5D-5L • SF-36 • TTO • VFQ-25	NR	NR	Mean (SD), median (IQR) • EQ-5D: 0.8 (0.2), 0.8 (0.7-1.0) • SF-6D: 0.7 (0.1), 0.7 (0.6-0.9) • TTO: 0.9 (0.2), 1.0 (0.8-1.0) • VFQ-25: 72.9 (22.1), 81.1 (57.8-91.6)	Consistent with reference case, as EQ-5D was reported by patients

Reference	Method of elicitation	Method of valuation	Mapping	Uncertainty around values	Utility values with confidence intervals	Consistency with reference case
	were willing to trade for perfect vision. The UVs were calculated from the maximum number of years that the person was willing to trade (Z) as follows: UV = (Y − Z)/Y. • Perceived visual function measure: VFQ-25					
Orme *et al.* (2012) [41]	Sourced from published literature	NR	NR	NR	UK-age specific population norms Quro QoL EQ-5D • 45-54: 0.85 • 55-64: 0.80 • 65-74: 0.78 • 75+: 0.73 Glaucoma - moderate: 0.72	Consistent with reference case, as EQ-5D was reported by patients

Reference	Method of elicitation	Method of valuation	Mapping	Uncertainty around values	Utility values with confidence intervals	Consistency with reference case
					Glaucoma - severe: 0.61	
Stein *et al.* (2012) [51]	Sourced from published literature	NR	NR	Uncertainty of the utility values was tested in sensitivity analysis	Utilities by glaucoma severity (range for sensitivity analysis) • Mild: 0.92 (0.8-0.99) • Moderate: 0.89 (0.87-0.95) • Severe: 0.86 (0.6-0.9) • Unilateral blindness: 0.47 (0.4-0.8) • Bilateral blindness: 0.26 (0.2-0.5) Utility score for experiencing side effects from laser procedure: 0.75	Not consistent with reference case, as EQ-5D was not reported by patients
van Gestel *et al.* (2014) [53]	• The relationship between VF and quality-of-life was based on a cross sectional study of random stratified samples of OHT and POAG patients from seven hospitals in The Netherlands. The impact of VF loss on HRQoL scores	• Generic HRQoL instruments (EQ-5D and Health Utilities Index mark 3) • Vision-specific National Eye Institute Visual Functioning Questionnaire (VFQ-25) • Glaucoma-specific Glaucoma	NR	NR	• Initial utility value: 0.88 • Side effects disutility: 0.101 • Cataract disutility: 0.065 • Each dB loss in Mean Deviation: 0.011	Consistent with reference case, as EQ-5D was reported by patients

Reference	Method of elicitation	Method of valuation	Mapping	Uncertainty around values	Utility values with confidence intervals	Consistency with reference case
	was analysed with multiple linear regression analyses including VF, cataract and side effects. • MD values of an HFA VF within 1 year were available for 72%. In another 8% of the cases, the MD values were calculated with existing formulas from the Octopus of VF within 1–2 years. For another 7% of the patients, MD values were calculated from older HFA 30-2/ 24-2 tests and/or recent 10-2 tests. Seven per cent of the patients	Quality-of-Life Questionnaire (GQL-15) • Questions on medication side effects				

Reference	Method of elicitation	Method of valuation	Mapping	Uncertainty around values	Utility values with confidence intervals	Consistency with reference case
	had MD values estimated based on other VF measurements, like 76 point screening or peritest. Four per cent had no VF. MD values for these patients (all POAG patients) were imputed based on worst-case imputation, as leaving out patients with missing MD values was not an option since this might have biased the results. • Side effect score was entered into the regression model as a continuous number					

Reference	Method of elicitation	Method of valuation	Mapping	Uncertainty around values	Utility values with confidence intervals	Consistency with reference case
	between 0 and 320, which is the cumulative score of two rating scales, pertaining to frequency (0–5) and severity (0–4), over 16 common side effects of glaucoma medication. For the disease progression model, the continuous side effect score was converted into a binary parameter (yes/no) representing the presence of a level of side effects that would prompt a change of medication. The cut-off point was set at a side effect score of 50, as					

Reference	Method of elicitation	Method of valuation	Mapping	Uncertainty around values	Utility values with confidence intervals	Consistency with reference case
	this was the average side effect score of patients in the observational study that indicated that side effects of medication impacted their quality-of-life 'Much' or 'Very much'. The coefficient for the continuous side effects score was multiplied by 50, which resulted in the 0.101 decrement in utility as a result of side effects in the model.					

Abbreviations: EQ-5D – Euro-QoL five-dimensions; EQ-5D-5L – EuroQoL five-dimensions five-level; GQL-15 – Glaucoma Quality of Life-15 Questionnaire; HFA – Humphrey field analyser; HRQoL – Health-related quality of life; IQR – Interquartile range; MD – Mean deviation; NR – Not reported; SD – Standard deviation; SF-36 – 36-Item Short Form Survey Instrument; TTO – Time trade-off; VF – Visual field; VFQ-25 – Visual Function Questionnaire 25

Summary of cost and resource studies publications

Table 67: Summary of UK cost and resource use publications identified from the targeted searches (n=4)

Study name	Hommer *et al.* 2008[89]	Holmstrom *et al.* 2006[42]	Orme *et al.* 2012[41]	Kobelt *et al.* 1999[40]
Country of study	UK, Spain, Italy, Norway, and Sweden	UK, Germany, Italy, Spain, France	UK	UK, France
Date of study	2007	2006	2012	1997
Applicability to clinical practice in England	Applicable	Applicable	Applicable	Applicable
Patient population	Patients with OAG or OHT	Patients with POAG	Patients with mild to moderate POAG or OHT (no visual field loss)	Patients with newly diagnosed POAG or OHT that were initially treated with beta-blocker monotherapy
Cost and resource use valuations used in the study	• Costs: Total costs per 3 months on treatment, medication costs per month, clinical ophthalmologist visit costs • Resource use: Ophthalmologist visit	• Costs: Medication (bimatoprost 0.03%, latanoprost 0.005%, timolol 0.5%) • Resource use: Ophthalmologist visit	• Costs: Monthly treatment acquisition cost by treatment line, resource use unit costs, economic results from the POAG model by treatment strategy including average cumulative results per patient and costs over time • Resource use: Number of follow-ups in a lifetime, first year and second year	• Costs: Laser surgery (ALT), trabeculectomy, ophthalmologist visit, diagnostic test unit costs, timolol, standard treatment, timolol with pilocarpine, dorzolamide, latanoprost, brimonidine • Resource use: NR
Costs for use in the economic analysis	Cost of clinical ophthalmologist visit • First visit UK: €136.44 (£102.00)	Medication • Bimatoprost 0.03% 3ml UK: £11.46, Germany: €24.23	Monthly treatment acquisition cost by treatment line • First line Latanoprost: £12.48 Bimatoprost: £10.30	Per unit or month • Laser surgery (ALT): France: FF 1044.63 UK: £175

Study name	Hommer *et al.* 2008[89]	Holmstrom *et al.* 2006[42]	Orme *et al.* 2012[41]	Kobelt *et al.* 1999[40]
	Sweden: €161.26 (1531.00 (SEK)) Norway: €55.07 (443.00 (NOK)) Italy: €20.66 Spain: €45.90 • Follow-up visit UK: €80.26 (£60.00) Sweden: €91.11 (865.00 (SEK)) Norway: €50.59 (407.00 (NOK)) Italy: €20.66 Spain: €45.90 Medication prices per month (including VAT) • BT (bimatoprost 0.03% and timolol 0.5%) UK: €16.75 (£12.53) Sweden: €22.39 (212.50 (SEK)) Norway: €23.42 (188.56 (NOK)) Italy: €24.47 Spain: €23.21 • TT (travoprost 0.004% and timolol 0.5%) UK: €16.76 (£12.54)	Italy: €20.74 Spain: €20.35 France: €19.63 • Latanoprost 0.005% 2.5ml UK: £13.14, Germany: €25.33, Italy: €20.74 Spain: €21.53 France: €17.25 • Timolol 0.5% 5ml: UK: £3.64 Germany: €10.94 Italy: €3.25 Spain: €4.73 France: €7.54 • Full visits at the ophthalmologist: UK: £38.00 Germany: €24.19, Italy: €23.00 Spain: €50.00 France: €23.00 • Follow-up visits at the ophthalmologist: UK: £28.50, Germany: €24.19 Italy: €18.00 Spain: €50.00 France: €23.00	Travoprost: £10.17 • Second line If poor tolerance – timolol: £1.99 If poor IOP control – latanoprost and timolol: £14.32 If poor IOP control – bimatoprost and timolol: £13.95 If poor IOP control – travoprost and timolol: £12.79 • Third line If poor tolerance – dorzolamide and timolol: £10.05 If poor IOP control – latanoprost, dorzolamide and timolol: £20.65 If poor IOP control – bimatoprost, dorzolamide and timolol: £20.28 If poor IOP control – Travoprost, dorzolamide and timolol: £19.12 Resource use unit costs • Outpatient visit (first follow-up): £93/visit	• Trabeculectomy: France: FF 9860.00 UK: £1262.84 • Ophthalmologist visit: France: FF 150 UK: £12.56 • Diagnostic tests: France: FF 179.64 UK: £28.82 • Timolol: France: FF68.44 UK: £5.82 • Standard treatment: France: FF65.89 UK: £3.99 • Timolol with pilocarpine: France: FF74.82 UK: NR • Dorzolamide: France: FF97.33 UK: £9.31 • Latanoprost: France: FF129.70 UK: £16.00 • Brimonidine: France: NR UK: £10.80

Study name	Hommer *et al.* 2008[89]	Holmstrom *et al.* 2006[42]	Orme *et al.* 2012[41]	Kobelt *et al.* 1999[40]
	Sweden: €22.39 (212.50 (SEK)) Norway: €23.61 (190.00 (NOK)) Italy: €24.47 Spain: €23.42 • LT (latanoprost 0.005% and timolol 0.5%) UK: €20.14 (£15.07) Sweden: 24.04 (228.17 (SEK)) Norway: €25.29 (203.52 (NOK)) Italy: €25.60 Spain: €23.88 Total costs per 3 months visit • BT (bimatoprost 0.03% and timolol 0.5%) UK: €266.97 (£199.59) Sweden: €319.47 (3033.50 (SEK)) Norway: €176.00 (1415.69 (NOK)) Italy: €116.66 Spain: €161.43		• Outpatient visit (subsequent follow-up): £87/visit Additional consultancy time for treatment switch: • Additional consultant time: £175/hour, £58/visit • Additional nurse time: £40/hour, £13/visit • Additional optometrist time: £40.50/hour, £14/visit • Total excess visit costs: £85/visit Surgery • Trabeculectomy: £996/procedure and /patient • Additional outpatient visits pre/post-surgery: £435/patient Annual cost of low vision • Non-treatment related cost of glaucoma: £725/patient • Care of blind/partially sighted patient: £8,538/patient Economic results from the POAG model by treatment strategy –	

Study name	Hommer *et al.* 2008[89]	Holmstrom *et al.* 2006[42]	Orme *et al.* 2012[41]	Kobelt *et al.* 1999[40]
	• TT (travoprost 0.004% and timolol 0.5%) UK: €267.022 (£199.62) Sweden: €319.47 (3033.50 (SEK)) Norway: €176.52 (1420.00 (NOK)) Italy: €116.66 Spain: €162.06 • LT (latanoprost 0.005% and timolol 0.5%) UK: €277.24 (£207.21) Sweden: 324.44 (3080.50 (SEK)) Norway: €181.56 (1460.55 (NOK)) Italy: €119.36 Spain: €163.44		average cumulative results per patient 1. Latanoprost first line Medical therapy costs: • First line: £303.13 • Second line: £246.86 • Third line: £227.17 • Subtotal cost of medical therapy (all lines): £777.16 Follow-up: • Scheduled follow-up visits: £598.50 • Additional follow-up visits: £190.38 Other costs: • Surgery: £112.04 • Long-term cost of low vision: £4,407.49 • Total cost: £6,086.40 2. Bimatoprost first line Medical therapy costs: • First line: £183.11 • Second line: £93.66 • Third line: £208.60 • Subtotal cost of medical therapy (all lines): £485.36 Follow-up: • Scheduled follow-up visits: £547.46	

Study name	Hommer *et al.* 2008[89]	Holmstrom *et al.* 2006[42]	Orme *et al.* 2012[41]	Kobelt *et al.* 1999[40]
			• Additional follow-up visits: £236.14 Other costs: • Surgery: £190.68 • Long-term cost of low vision: £4,699.55 • Total cost: £6,160.04 3. Travoprost first line Medical therapy costs: • First line: £193.73 • Second line: £86.52 • Third line: £207.72 • Subtotal cost of medical therapy (all lines): £487.98 Follow-up: • Scheduled follow-up visits: £552.81 • Additional follow-up visits: £247.45 Other costs: • Surgery: £198.95 • Long-term cost of low vision: £4,723.63 • Total cost: £6,211.70 Analysis of costs over time 1. Latanoprost first line • Cost per day of medical treatment: £0.82	

Study name	Hommer *et al.* 2008[89]	Holmstrom *et al.* 2006[42]	Orme *et al.* 2012[41]	Kobelt *et al.* 1999[40]
			• Costs in first year: £520.36 • Costs in second year: £489.00 2. Bimatoprost first line • Cost per day of medical treatment: £0.85 • Costs in first year: £525.48 • Costs in second year: £479.71 3. Travoprost first line • Cost per day of medical treatment: £0.88 • Costs in first year: £543.56 Costs in second year: £488.49	
Resource use values for use in the economic analysis	• 2 ophthalmologist visits in the first 3 months, with a third if experiencing adverse events	• 2 full visits at the ophthalmologist and 2 follow-up visits, as well as 2 extra visits if the specified level of IOP was not reached. If therapy was changed due to persisting adverse events, then the patient had an additional visit to the ophthalmologist	Frequency of scheduled visits • First visit after starting/switching treatment (high risk patients): after 1 month • First visit after starting/switching treatment (low risk patients): after 3 months • Subsequent visits if patient stable on treatment (high risk	NR

Study name	Hommer *et al.* 2008[89]	Holmstrom *et al.* 2006[42]	Orme *et al.* 2012[41]	Kobelt *et al.* 1999[40]
			patients): every 12 months • Subsequent visits if patient stable on treatment (low risk patients): every 18 months Surgery • Additional outpatient visits pre/post-surgery: 5 visits • Surgery rate per month (low risk patients): 0.2% • Surgery rate per month (high risk patients): 0.6% Number of follow-ups (lifetime): • Latanoprost first line: 7.41 • Bimatoprost first line: 7.05 • Travoprost first line: 7.13 Number of follow-ups in first year: • Latanoprost first line: 1.75 • Bimatoprost first line: 1.90 • Travoprost first line: 1.99	

Study name	Hommer *et al.* 2008[89]	Holmstrom *et al.* 2006[42]	Orme *et al.* 2012[41]	Kobelt *et al.* 1999[40]
			Number of follow-ups in second year: • Latanoprost first line: 1.25 • Bimatoprost first line: 1.31 Travoprost first line: 1.32	

Abbreviations: ALT – Argon laser trabeculoplasty; BT – Bimatoprost/timolol; LT – Latanoprost/timolol; NR – Not reported; OAG – Open-angle glaucoma; OHT – Ocular hypertension; POAG – Primary open-angle glaucoma; TT – Travoprost/timolol; UK – United Kingdom

Table 68: Summary of non-UK cost and resource use publications identified from the targeted searches (n=18) (Part A)

Study name	Berdahl *et al.* 2017[96]	Bernard *et al.* 2003[43]	van Gestel *et al.* 2014[53]	Stewart *et al.* 2008[52]	Rouland *et al.* 2003[50]
Country of study	US	France	The Netherlands	US	France, Italy, Portugal, and Spain
Date of study	2017	2003	2014	2008	2003
Applicability to clinical practice in England	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Patient population	Patients with OAG not adequately controlled by one medication	Patients with OAG or OHT	Patients with OHT	Patients with OHT	Patients with OHT and/or POAG who had not responded to or could not tolerate beta-blocker therapy
Cost and resource use valuations used in the study	• Costs: Cumulative total costs over 5 years for initiating treatment with medications	• Costs: Cost of ophthalmologist visits, prescriptions per 28 days, surgery per patient	• Costs: Treatment costs, resource use costs, productivity loss costs, health	• Costs: Procedure unit costs, health economic total costs	• Costs: Cost of anti-glaucoma drugs, CAI regimens, ophthalmologist visits

Study name	Berdahl *et al.* 2017[96]	Bernard *et al.* 2003[43]	van Gestel *et al.* 2014[53]	Stewart *et al.* 2008[52]	Rouland *et al.* 2003[50]
	only, SLT, or iStent procedures. Total costs included drug, procedures, and complication costs • Resource use: NR	assuming both eyes • Resource use: Ophthalmologist visit	economic total costs • Resource use: NR	• Resource use: NR	• Resource use: CAI monotherapy prescription rate
Costs for use in the economic analysis	Treatment costs • 1 medication: $495.01 • 2 medications: $960.66 • 3 medications: $1020.04 • 4 medications: $2086.41 Procedures • iStent: $2711.27 • SLT: $396.39 • Filtering surgery: $3783.32	Ophthalmologist visit • Initial assessment visit in the model: €40.88 • Subsequent assessment visits in the model: €36.05 Cost of prescription • Beta-blocker first-line therapy: €5.57 • Usual care second line: €11.87 • Subsequent therapies: €15.02	Resource use unit costs: • Beta-blocker: €6/month • PGA: €20.20/month • CAI: €13.90/month • Alpha-adrenergic agonist: €14/month • Ophthalmologist consultation: €65 • Visual field measurement: €133 (€266 in case of progression) • LT: €75	Procedure unit costs: • Comprehensive visit: $109 • Central corneal thickness: $28 • Follow-up visit: $57 • Gonioscopy: $36 • IOP: $35 • Optic disc imaging: $82 • Refraction: $20 • Annual cost of glaucoma medication: $492 • Automated visual field: $76	Cost per treatment of anti-glaucoma drugs in France • Timolol: €7.02 • Latanoprost: €20.98 • Dorzolamide: €14.08 • Brinzolamide: €14.74 Cost per treatment of anti-glaucoma drugs in Italy • Timolol: €5.44 • Latanoprost: €24.53 • Dorzolamide: €14.51

Study name	Berdahl *et al.* 2017[96]	Bernard *et al.* 2003[43]	van Gestel *et al.* 2014[53]	Stewart *et al.* 2008[52]	Rouland *et al.* 2003[50]
	Complications 1st following year • iStent: $0.00 • SLT: $0.00 • Filtering surgery: $1021.38 Complications all other subsequent years • iStent: $0.00 • SLT: $0.00 • Filtering surgery: $363.37 Cumulative total costs over 5 years • Medications only: $6217.08 • SLT: $4729.85 • iStent: $4420.38	Latanoprost first-line therapy: €11.49 Usual care second line: €11.77 Subsequent therapies: €13.22 Cost of surgery • Acute cost: €1120	• Trabeculectomy: €1,214 (+1 ophthalmologist consultation) • Tube implantation: €1,714 (+1 ophthalmologist consultation) • Cataract surgery: €1,400 • Paid household help: €37/month (if MD < -10 dB) • Homecare nursing: €159/month (if MD < -10 dB) • Family help: €56/month (if MD < -15 dB) • Homecare grooming: €103/month (if MD < -15 dB) • Retirement home: €80/month (if MD < -20 dB) • Nursing home: €130/month (if MD < -20 dB)	Baseline costs over 5 years: • No treatment arm: $2,467 • Treatment arm: $5,001	• Brinzolamide: €14.98 Cost per treatment of anti-glaucoma drugs in Portugal • Timolol: €5.99 • Latanoprost: €23.19 • Dorzolamide: €13.73 • Brinzolamide: €13.73 (hypothetical price) Cost per treatment of anti-glaucoma drugs in Spain • Timolol: €3.43 • Latanoprost: €23.64 • Dorzolamide: €13.25 • Brinzolamide: €13.91 Daily cost of each CAI regimen – monotherapy in France

Study name	Berdahl *et al.* 2017[96]	Bernard *et al.* 2003[43]	van Gestel *et al.* 2014[53]	Stewart *et al.* 2008[52]	Rouland *et al.* 2003[50]
			• Informal care: €20/month (if MD < -5 dB) • Low vision services: €1-5/month • Transport to ophthalmologist: €4.90/visit (if MD > -10 dB), €8.90/visit (if MD < -10 dB) • Transport to pharmacy: €1.50/visit (if MD > -10 dB), €2.60/visit (if MD < -10 dB) • Low vision aids: €325 (once) if MD progresses below -15 dB • Productivity loss: €3,029 (once) if MD progresses below -15 dB while the patient is less than 65 years Health economic costs:		• Brinzolamide bid: €0.53 • Brinzolamide tid: €0.57 • Dorzolamide tid: €0.67 Daily cost of each CAI regimen – monotherapy in Italy • Brinzolamide bid: €0.54 • Brinzolamide tid: €0.58 • Dorzolamide tid: €0.69 Daily cost of each CAI regimen – monotherapy in Portugal • Brinzolamide bid: €0.49 • Brinzolamide tid: €0.53 • Dorzolamide tid: €0.71 Daily cost of each CAI regimen – monotherapy

Study name	Berdahl *et al.* 2017[96]	Bernard *et al.* 2003[43]	van Gestel *et al.* 2014[53]	Stewart *et al.* 2008[52]	Rouland *et al.* 2003[50]
			• Total costs over 10 years: • Treatment arm 1: watchful waiting • Undiscounted: €2,302 • Discounted: €1,891 • Treatment arm 2: direct treatment • Undiscounted: €3,415 • Discounted: €2,844 Total costs over lifetime (mean 26 years): • Treatment arm 1: watchful waiting • Undiscounted: €18,327 • Discounted: €7,722 • Treatment arm 2: direct treatment		in Spain • Brinzolamide bid: €0.50 • Brinzolamide tid: €0.54 • Dorzolamide tid: €0.63 Daily cost – combination therapy in France • Brinzolamide bid: €0.53 • Dorzolamide bid: €0.50 Daily cost – combination therapy in Italy • Brinzolamide bid: €0.54 • Dorzolamide bid: €0.52 Daily cost – combination therapy in Portugal • Brinzolamide bid: €0.49

Study name	Berdahl *et al.* 2017[96]	Bernard *et al.* 2003[43]	van Gestel *et al.* 2014[53]	Stewart *et al.* 2008[52]	Rouland *et al.* 2003[50]
			• Undiscounted: €14,343 • Discounted: €7,073		• Dorzolamide bid: €0.53 Daily cost – combination therapy in Spain • Brinzolamide bid: €0.50 • Dorzolamide bid: €0.47 Cost per treatment of ophthalmologist visits • France: €22.90 • Italy: €41.32 • Portugal: €49.13 Spain: €84.82
Resource use values for use in the economic analysis	NR	Ophthalmologist visit frequency • Patients receiving a new therapy: 3 months • Patients maintained on current therapy: 4 months	NR	NR	CAI monotherapy prescription rate (%) • France: 18 • Italy: 48 • Portugal: 14 • Spain: 16.5

Abbreviations: CAI – Carbonic anhydrase inhibitors; MD – Mean deviation; NR – Not reported; OAG – Open-angle glaucoma; OHT – Ocular hypertension; PGA – Prostaglandin analogue; POAG – Primary open-angle glaucoma; SLT - Selective laser trabeculoplasty; UK – United Kingdom; US – United States

Table 69: Summary of non-UK cost and resource use publications identified from the targeted searches (n=18) (Part B)

Study name	**Stewart *et al.* 2002**[97]	**Cantor *et al.* 2008**[98]	**Stein *et al.* 2012**[51]	**Cottle *et al.* 1988**[45]	**Berenson *et al.* 2011**[99]
Country of study	US	US	US	Canada	US
Date of study	2002	2008	2012	1988	2011
Applicability to clinical practice in England	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Patient population	Patients with OAG or OHT who were prescribed a topical beta-adrenergic blocker as monotherapy then switched to latanoprost 0.005% once daily or had either brimonidine 0.2% twice daily or latanoprost added and had at least 1 follow-up visit after the change in therapy.	Patients with POAG whose intra-ocular pressures were not adequately controlled by two medications	Patients aged 60 years old with mild OAG	Patients with newly diagnosed and untreated POAG	Patients with POAG
Cost and resource use valuations used in the study	• Costs: Treatment cost per person per month • Resource use: Visits per person per month, number of medicine changes per person per month	• Costs: Medication, laser trabeculoplasty, surgery • Resource use: NR	• Costs: Medications, laser surgery, incisional surgery, initial evaluation, follow-up	• Costs: Parasympathomimetic (pilocarpine 0.5%, 1.0%, 2.0%), beta-blocker (timolol 0.25%, 0.5%) • Resource use: NR	• Costs: Unit costs, cost-offset analysis results, budget impact results

Study name	Stewart *et al.* 2002[97]	Cantor *et al.* 2008[98]	Stein *et al.* 2012[51]	Cottle *et al.* 1988[45]	Berenson *et al.* 2011[99]
			evaluation, low vision services, side effects • Resource use: NR		
Costs for use in the economic analysis	Latanoprost monotherapy • Cost/person/month pre-enrolment (beta-blocker only): $66.71 ± 99.80 (33.44-99.99) • Cost/person/month post-enrolment: $53.63 ± 11.95 (49.64-57.61) Latanoprost + beta- blocker • Cost/person/month pre-enrolment (beta-blocker only): $53.98 ± 19.12 (49.55-58.51) • Cost/person/month post-enrolment: $83.19 ± 79.29 (64.82-101.56) Brimonidine + beta- blocker • Cost/person/month pre-enrolment (beta-blocker only): $75.67	5 year treatment costs • Medication only: $6571 • Laser trabeculoplasty: $4838 • Surgery: $6363 Cost/year for first line prostaglandin analogue • Bimatoprost (Lumigan): 2.5ml $500, 5 ml $614, 7.5ml $618 • Travoprost (Travatan): 2.5ml $508, 5ml $509 • Travoprost (Travatan Z): 2.5ml $553, 5ml $616	Medication • PGAs: $330 (0-1000) • Alpha-agonists: $1,242 (0-1500) • Beta-blockers: $435 (0-500) Surgery • Laser surgery (Laser trabeculoplasty): $677 (100-2000) • Incisional surgery (trabeculectomy): $2,824 (1000-4000) Initial evaluation • Visit: $190 (100-200)	Cost per month per eye • Pilocarpine 2% qid: $1.04 • Pilocarpine 1% qid: $1.11 • Timolol 0.25% bid: $3.47 • Timolol 0.5% bid: $4.14 • Dipivifrin 0.1% bid: $2.45 • Ocusert Pilo-40 1 per week: $11.64 • Epinephrine 1% bid: $1.65 • Acetazolamide 250mg qid: $13.35 • Methazolamide 50mg bid: $16.20-18.60 (from sample of retail pharmacies in Phoenix area in 1987)	Monthly cost • Bimatoprost: $84.56 • Travoprost: $84.96 • Latanoprost: $82.67 • Generic latanoprost: $66.14 Dispensing fee • Bimatoprost, Travoprost and latanoprost: $2.00 • Generic latanoprost: $3.00 Copay • Bimatoprost, Travoprost and

Study name	Stewart *et al.* 2002[97]	Cantor *et al.* 2008[98]	Stein *et al.* 2012[51]	Cottle *et al.* 1988[45]	Berenson *et al.* 2011[99]
	± 92.45 (44.85-106.50) • Cost/person/month post-enrolment: $106.20 ± 134.59 (61.32-151.07)	• Latanoprost (Xalatan): 2.5ml $536 Second-line non-selective beta-blockers • Timolol maleate (Isatolol 0.5%): 5ml $343 • Timolol maleate (Timoptic 0.5%): 5ml $230, 10ml $231 • Timolol maleate (Timoptic 0.5% XE): 5ml $261 • Carteolol 1.0%: 5ml $226, 10ml $210, 15ml $198 • Levobunolol 0.5%: 5ml $178, 10ml	• Diagnostic testing: $207 (100-300) Follow-up evaluation • Visit: $111 (50-150) • Diagnostic testing: $123 (100-150) Low vision services • Unilateral low vision: $1,000 (500-4000) • Bilateral low vision: $2,000 (1000-8000) Side effects of laser trabeculoplasty: $1000 (0-2000) Base case results • Costs over 25 years: • Untreated group: $2,700		latanoprost: $25.00 • Generic latanoprost: $10.00 Pharmacy discount • Bimatoprost: $12.68 • Travoprost: $12.74 • Latanoprost: $12.40 • Generic latanoprost: $11.24 Annual cost per patient to plan • Bimatoprost: $890.93 • Travoprost: $896.45 • Latanoprost: $864.85 • Generic latanoprost: $844.61

Study name	Stewart *et al.* 2002[97]	Cantor *et al.* 2008[98]	Stein *et al.* 2012[51]	Cottle *et al.* 1988[45]	Berenson *et al.* 2011[99]
		$183, 15ml $190 • Metipranalol 0.3%: 5ml $183, 10ml $152 • Timolol 0.5% gel: 5ml $235 • Timolol maleate 0.5%: 5ml $156, 10ml $159, 15ml $151 Third-line alpha-agnoist • Brimonidine (Alphagan P 0.15%): 5ml $838, 10ml $874, 15ml $856 • Brimonidine 0.2%: 5ml $559, 10ml $529, 15ml $574 Fourth-line carbonic anhydrase inhibitors	• LTP group: $13,788 • PGA group: $18,101		Direct costs (all payers) • Laser trabeculoplasty (argon/selective): $1,508.00 • Office visits: $76.50 • Visual field tests: $95.00 • Additional glaucoma medications (non-PGA): $514.56 Cost-offset analysis results - Base case early glaucoma (presenting MD score -4dB) • Cost per progression – bimatoprost, travoprost, latanoprost: $4,009 • Total cost of progression – bimatoprost: $2,525,670

Study name	Stewart *et al.* 2002[97]	Cantor *et al.* 2008[98]	Stein *et al.* 2012[51]	Cottle *et al.* 1988[45]	Berenson *et al.* 2011[99]
		• Brinzolamide (Azopt): 5ml $566, 10ml $596, 15ml $546 • Dorzolamide (Trusopt): 10ml $615			• Total cost of progression – travoprost: $3,070,894 • Total cost of progression – latanoprost: $3,070,894 • Cost savings from delayed or avoided progression given exclusive treatment with bimatoprost rather than Travoprost or latanoprost: $545,224 Base case advanced glaucoma (presenting MD score -10dB) • Cost per progression – bimatoprost, travoprost, latanoprost: $4,543 • Total cost of progression –

Study name	Stewart *et al.* 2002[97]	Cantor *et al.* 2008[98]	Stein *et al.* 2012[51]	Cottle *et al.* 1988[45]	Berenson *et al.* 2011[99]
					bimatoprost: $2,862,090 • Total cost of progression – travoprost: $3,479,938 • Total cost of progression – latanoprost: $3,479,938 • Cost savings from delayed or avoided progression given exclusive treatment with bimatoprost rather than Travoprost or latanoprost: $617,848 Budget impact results - Base case analysis for early glaucoma population. Total cost for all PGAs over 7 years • Default market share: $109,647,980

Study name	Stewart *et al.* 2002[97]	Cantor *et al.* 2008[98]	Stein *et al.* 2012[51]	Cottle *et al.* 1988[45]	Berenson *et al.* 2011[99]
					• Scenario A: switching all bimatoprost patients to generic latanoprost: $108,992,530 • Scenario B: switching all travoprost patients to generic latanoprost: $108,773,450 Base case analysis for advanced glaucoma population. Total cost for all PGAs over 7 years • Default market share: $131,079,830 • Scenario A: switching all bimatoprost patients to generic latanoprost: $130,440,330 • Scenario B: switching all

Study name	Stewart *et al.* 2002[97]	Cantor *et al.* 2008[98]	Stein *et al.* 2012[51]	Cottle *et al.* 1988[45]	Berenson *et al.* 2011[99]
					travoprost patients to generic latanoprost: $130,205,250
Resource use values for use in the economic analysis	Latanoprost monotherapy (mean ± SD) • Number of visits/person/month: 0.36 ± 0.20 • Total number of visits: 3.8 ± 2.0 • Number of medicine changes/person/month: 0.01 ± 0.03 Latanoprost + beta-blocker (mean ± SD) • Number of visits/person/month: 0.38 ± 0.20 • Total number of visits: 4.2 ± 1.5 • Number of medicine changes/person/month: 0.01 ± 0.06	NR	NR	NR	NR

Abbreviations: dB – Decibel; MD – mean deviation; NR – Not reported; OAG – Open-angle glaucoma; OHT – Ocular hypertension; POAG – Primary open-angle glaucoma; SD – Standard deviation; UK – United Kingdom; US – United States

Table 70: Summary of non-UK cost and resource use publications identified from the targeted searches (n=18) (Part C)

Study name	Kobelt *et al.* 2010[100]	Lee *et al.* 2006[101]	Peeters *et al.* 2012[37]	van Gestel *et al.* 2012[54]	Kymes *et al.* 2010[47]
Country of study	France	Canada	The Netherlands	The Netherlands	US
Date of study	2010	2006	2012	2012	2010
Applicability to clinical practice in England	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Patient population	Patients with POAG and OHT with insufficiently controlled IOP starting first or second line prostaglandin treatment	Patients with OAG, aged 65 years or more	Patients with POAG	Patients with POAG	Patients with POAG, aged 65 or older
Cost and resource use valuations used in the study	• Costs: Hospitalisation, surgical interventions (outpatient and inpatient), argon laser trabeculoplasty, consultations (outpatient, private practice, visual field), private practice, medication • Resource use: Number of patients completing 4 years for consultations and examinations, inpatient admissions, inpatient surgery, outpatient surgery	• Costs: Glaucoma medication costs, cost-comparison, cost difference over 6 years • Resource use: Glaucoma medications by class prescribed to Ontario patients and frequency of mono-, bi- and tri-drug therapies for treatment of glaucoma in Ontario	• Costs: Treatment cost, visits, transportation • Resource use: NR	• Costs: Direct medical costs (ophthamologist visits, VF measurements, medication, surgery, home care, low-visit rehabilitation and aids, retirement and nursing home), Direct nonmedical costs (transportation to healthcare	• Costs: Incidence costs, prevalence costs and drug costs for the occurrence of events reported to be associated with visual impairment (split by gender)

Study name	Kobelt *et al.* 2010[100]	Lee *et al.* 2006[101]	Peeters *et al.* 2012[37]	van Gestel *et al.* 2012[54]	Kymes *et al.* 2010[47]
				providers, costs for informal care), Indirect nonmedical costs (production losses) • Resource use: NR	• Resource use: Annual incidence (per 1000) of comorbid and other events
Costs for use in the economic analysis	Hospitalisation (per day): €643 Surgical interventions (diagnosis related group) • Inpatient: €2888 • Outpatient: €948 Argon laser trabeculoplasty (outpatient): €125 Consultations • Outpatient clinic: €28 • Private practice: €43 • Visual field (per eye): €33 Medication (month) • Xalatan: €17.61 • Xalacom: €23.24	Annual cost of glaucoma medication by class of drug - Combination drugs. Dorzolamide-timolol (5ml) • Cost/bottle: $25.00 • Cost/year: $260.98 • Pharmacy adjusted cost/year: $276.52 Average annual cost to OHIP: • Cost/year: $288.64 • Pharmacy adjusted cost/year: $305.74 CAIs. Dorzolamide (5ml) • Cost/bottle: $16.50 • Cost/year: $216.98 • Pharmacy adjusted cost/year: $262.55	Costs per patient within 15 months of therapy • Latanoprost IOP 25 mm HG: €367 • Timolol IOP 25 mm HG: €469 • Latanoprost IOP 30 mm HG: €441 • Timolol IOP 30 mm HG: €496 Treatment cost • Timolol: 5.10 €/month	Total costs • Usual care: €37,328 • No care: €67,002 • Initial medication: €37,401 • Target pressure: €34,026 • VF 6 months: €38,765 • VF 24 months: €37,040 Treatment cost • Beta-blocker: € 6.00/month	Male (Incidence; Prevalence; Drug) • Depression: $31,341; $10,889; $3936 • Dementia: $23,730; $11,544; $3231 • Hip fracture: $31,828; $15,022; $3324 • Any fracture (excluding hip): $20,635; $9744; $3481 • Nursing home:

Study name	Kobelt *et al.* 2010[100]	Lee *et al.* 2006[101]	Peeters *et al.* 2012[37]	van Gestel *et al.* 2012[54]	Kymes *et al.* 2010[47]
	• Travatan: €20.04 • Lumigan: €20.04 • Alphagan: €13.83 • Trusopt: €13.99 • Cosopt: €18.95 • Betoptic: €5.01	Brinzolamide (5ml) • Cost/bottle: $15.70 • Cost/year: $232.95 • Pharmacy adjusted cost/year: $281.87 Average cost • Cost/bottle: $16.10 • Cost/year: $224.97 • Pharmacy adjusted cost/year: $272.21 Average annual cost to OHIP • Cost/year: $249.03 • Pharmacy adjusted cost/year: $301.00 Alpha-agonists covered by OHIP. Brimonidine 0.2% (5ml) • Cost/bottle: $16.50 • Cost/year: $211.43 • Pharmacy adjusted cost/year: $188.20 Average cost • Cost/bottle: $16.50	• Latanoprost: 18.67 €/ month • Dorzolamide: 12.86 €/ month • Brimonidine: 14.32 €/ month • Timolol + Latanoprost (add-on): 22.79 €/ month • Timolol + Dorzolamide (add-on): 17.59 €/ month • Outpatient visit (15 min): 27.57 € • Outpatient visit (10 min) :23.85 € • Perimetry: 80.93 € • Laser: 279.42 €	• Prostaglandin analogue: € 20.20/month • Carbonic anhydrase inhibitor: € 13.90/ month • α2-adrenergic agonist: € 14.00/month • Ophthalmologist consultation: € 65 • Visual field measurement: € 133 (€ 266 in case of progression) • LT: € 75 • Trabeculectomy: € 1,214 (+ 1 ophthalmologist consultation) • Tube implantation: € 1,714 (+ 1 ophthalmologist consultation) • Cataract surgery: € 1,400	$48,679; $16,560; - • Skilled nursing facility: $47,792; $19,670; $3508 • Home healthcare: $23,401; $14,232; $3020 • Moderate visual impairment: $16,589; $9183; $2387 • Severe visual impairment or blindness: $24,496; $9599; $3841 Female (Incidence; Prevalence; Drug)

Study name	Kobelt *et al.* 2010[100]	Lee *et al.* 2006[101]	Peeters *et al.* 2012[37]	van Gestel *et al.* 2012[54]	Kymes *et al.* 2010[47]
		• Cost/year: $211.43 • Pharmacy adjusted cost/year: $188.20 Average annual cost to OHIP: • Cost/year: $234.14 • Pharmacy adjusted cost/year: $208.59 PGAs. Travoprost (2.5ml) • Cost/bottle: $26.50 • Cost/year: $189.66 • Pharmacy adjusted cost/year: $248.01 Latanoprost (2.5ml) • Cost/bottle: $26.00 • Cost/year: $194.47 • Pharmacy adjusted cost/year: $243.33 Average cost • Cost/bottle: $26.25 • Cost/year: $192.07 • Pharmacy adjusted cost/year: $245.67	• Transportation (per visit): 2.9 € • Glaucoma therapy: 450 € ⁄ year	• Paid household help: € 37 / month (if MD < -10 dB) • Homecare nursing: € 159 / month (if MD < -10 dB) • Family help: € 56 / month (if MD < -15 dB) • Homecare grooming: € 103 / month (if MD < -15 dB) • Retirement home: € 80 / month (if MD < -20 dB) • Nursing home: € 130 / month (if MD < -20 dB) • Informal care: € 20 / month (if MD < -5dB) • Low vision services: € 1-5 /month • Transport to ophthalmologist: € 4.90 / visit (if	• Depression: $18,135; $8552; $4177 • Dementia: $20,321; $8538; $3146 • Hip fracture: $35,130; $12,066; $3290 • Any fracture (excluding hip): $18,201; $7891; $3402 • Nursing home: $39,058; $12,807; - • Skilled nursing facility: $39,566; $16,329; $3462 • Home healthcare: $17,689;

Study name	Kobelt *et al.* 2010[100]	Lee *et al.* 2006[101]	Peeters *et al.* 2012[37]	van Gestel *et al.* 2012[54]	Kymes *et al.* 2010[47]
		Average annual cost to OHIP: • Cost/year: $212.84 • Pharmacy adjusted cost/year: $271.81 Beta-blockers • Timolol 0.25% (10ml) • Cost/bottle: $15.50 • Cost/year: $63.69 • Pharmacy adjusted cost/year: $77.06 Timolol 0.50% (10ml) • Cost/bottle: $18.60 • Cost/year: $76.42 • Pharmacy adjusted cost/year: $92.47 Timolol-XE 0.25% (5ml) • Cost/bottle: $16.30 • Cost/year: $75.98 • Pharmacy adjusted cost/year: $116.66 Timolol-XE 0.50% (5ml)		MD > -10 dB), € 8.90 / visit (if MD < -10 dB) • Transport to pharmacy: € 1.50 / visit (if MD > -10 dB), € 2.60 / visit (if MD < -10 dB) • Low vision aids: € 325 (once) if MD moves below -15 dB • Productivity loss: € 3,029 (once) if MD moves below -15 dB while the patients is younger than 65 years.	$12,351; $3876 • Moderate visual impairment: $17,486; $7492; $3892 • Severe visual impairment or blindness: $16,543; $9669; $3257

Study name	Kobelt *et al.* 2010[100]	Lee *et al.* 2006[101]	Peeters *et al.* 2012[37]	van Gestel *et al.* 2012[54]	Kymes *et al.* 2010[47]
		• Cost/bottle: $19.50 • Cost/year: $90.90 • Pharmacy adjusted cost/year: $139.56 Levobunolol 0.25% (10ml) • Cost/bottle: $11.76 • Cost/year: $79.78 • Pharmacy adjusted cost/year: $96.53 Levobunolol 0.50% (10ml) • Cost/bottle: $15.55 • Cost/year: $105.49 • Pharmacy adjusted cost/year: $127.64 Average cost • Cost/bottle: $16.20 • Cost/year: $82.04 • Pharmacy adjusted cost/year: $108.32 Average annual cost to OHIP: • Cost/year: $91.82 • Pharmacy adjusted cost/year: $120.72			

Study name	Kobelt *et al.* 2010[100]	Lee *et al.* 2006[101]	Peeters *et al.* 2012[37]	van Gestel *et al.* 2012[54]	Kymes *et al.* 2010[47]
		Pilocarpine HCL 2% (5ml) • Cost/bottle: $0.97 • Cost/year: $11.33 • Pharmacy adjusted cost/year: $13.71 Pilocarpine HCL 4% (5ml) • Cost/bottle: $1.10 • Cost/year: $12.85 • Pharmacy adjusted cost/year: $15.55 Average cost • Cost/bottle: $1.04 • Cost/year: $12.09 • Pharmacy adjusted cost/year: $14.63 Average annual cost to OHIP: • Cost/year: $14.87 • Pharmacy adjusted cost/year: $17.66			
Resource use values for use in the economic analysis	Consultations and exminations (both eyes) quantity mean (SD) • Consultations: 9.2 (3.0) • IOP measurements: 18.4 (5.9)	Glaucoma medications by class prescribed to Ontario patients. Mono-drug therapy - No. of prescriptions (%) • Prostaglandin: 221 (54)	NR	NR	Estimated in markov model by microsimulation - POAG cohort • Depression: 31.6

Study name	Kobelt *et al.* 2010[100]	Lee *et al.* 2006[101]	Peeters *et al.* 2012[37]	van Gestel *et al.* 2012[54]	Kymes *et al.* 2010[47]
	• Visual field (MD): 6.8 (5.4) • Cornea thickness: 2.7 (3.3) • Gonioscopy: 1.9 (3.0) • Diurnal IOP assess: 0.6 (1.4) • Photo nerve: 0.1 (0.7) • Photo disc: 0.8 (1.7) In patient admissions (no surgery) • Days: 0.22 • Inpatient srugery (both eyes) • Cataract: 0.02 (0.19) • Trabeculectomy: 0.01 (0.14) • Trabeculectomy/cataract: 0.02 (0.18) • Other: 0.03 (0.16) Outpatient surgery (both eyes) • Cataract: 0.08 (0.33) • Trabeculectomy: 0.03 (0.17) • Trabeculectomy/cataract: 0.01 (0.12)	• Beta-blocker: 126 (31) • CAI: 2 (0) • Dorzolamide/timolol: 38 (9) • Alpha-agonist: 13 (3) • Pilocarpine: 7 (2) Bi-drug therapy - No. of prescriptions (%) • Prostaglandin: 203 (42) • Beta-blocker: 114 (24) • CAI: 27 (6) • Dorzolamide/timolol: 84 (18) • Alpha-agonist: 39 (8) • Pilocarpine: 16 (3) Tri-drug therapy - No. of prescriptions (%) • Prostaglandin: 57 (31) • Beta-blocker: 27 (15)			• Dementia: 32.9 • Hip fracture:16.2 • Any fracture (excluding hip): 35.2 • Nursing home admission: 28.5 • Skilled nursing facility admission: 39.6 • Home healthcare service use: 62.1 • Moderate visual impairment: 8.3 • Severe visual impairment or blindness: 1.0

Study name	Kobelt *et al.* 2010[100]	Lee *et al.* 2006[101]	Peeters *et al.* 2012[37]	van Gestel *et al.* 2012[54]	Kymes *et al.* 2010[47]
	• Argon laser trabeculoplasty: 0.03 (0.20) • Other: 0.04 (0.24)	• CAI: 22 (12) • Dorzolamide/timolol: 23 (12) • Alpha-agonist: 44 (24) • Pilocarpine: 14 (7) Total occurrence of drug - No. of prescriptions (%) • Prostaglandin: 481 (45) • Beta-blocker: 267 (25) • CAI: 51 (5) • Dorzolamide/timolol: 145 (14) • Alpha-agonist: 96 (9) • Pilocarpine: 37 (2) Frequency of mono-, bi- and tri-drug therapies for treatment of glaucoma in Ontario • No. of patients (%) • Mono-drug therapy: 407 (57.6)			Control cohort (matched 1:1 with POAG cohort for age, gennder, race, Cetners for Medicare and Medicaid Services region) • Depression: 31.0 • Dementia: 33.9 • Hip fracture:16.7 • Any fracture (excluding hip): 34.3 • Nursing home admission: 27.7 • Skilled nursing facility admission: 39.6 • Home healthcare service use: 61.0

Study name	Kobelt *et al.* 2010[100]	Lee *et al.* 2006[101]	Peeters *et al.* 2012[37]	van Gestel *et al.* 2012[54]	Kymes *et al.* 2010[47]
		• Bi-drug therapy: 239 (33.8) • Tri-drug therapy: 61 (8.6) • Total number of patients: 707 (100)			• Moderate visual impairment: 4.2 • Severe visual impairment or blindness: 0.2

Abbreviations: CAI - Carbonic anhydrase inhibitors; dB – Decibel; IOP - Intraocular pressure; MD – Mean deviation; OAG – Open-angle glaucoma; OHT – Ocular hypertension; POAG – Primary open-angle glaucoma; SD – Standard deviation; US – United States; VF- Visual field

Table 71: Summary of non-UK cost and resource use publications identified from the targeted searches (n=18) (Part D)

Study name	Marchetti *et al.* 2001[48]	Rocchi *et al.* 1997[49]	Kymes *et al.* 2006[46]
Country of study	US	Canada	US
Date of study	2001	1997	2006
Applicability to clinical practice in England	Not applicable	Not applicable	Not applicable
Patient population	Patients with newly diagnosed or currently untreated OHT or OAG	Patients with POAG aged over 65 years	Patients with IOP ≥24 mmHg
Cost and resource use valuations used in the study	• Costs: First line brimonidine 0.2%, betaxolol 0.25% • Resource use: NR	• Costs: Dorzolamide, pilocarpine • Resource use: NR	• Costs: Average cost of medication for one year, cataract surgery • Resource use: NR
Costs for use in the economic analysis	Expected costs as a primary therapy • Brimonidine: $301.37 • Betaxolol: $328.19	Acquisition price • Dorzolamide: $16.50 • Pilocarpine: $3.54	• Average cost of medication for one year : $465.31 • Average cost of travel to office visit: $11.12 • Patient's time for office visit: $31.64 • Cost of cataract surgery: $2525
Resource use values for use in the economic analysis	NR	NR	NR

Abbreviations: IOP – Intraocular pressure; NR – Not reported; OHT – Ocular hypertension; POAG – Primary open-angle glaucoma; UK - United Kingdom; US – United States

Appendix B

Methods and outcomes of studies included in the NMA

Table 72: DuBiner et al. (2001) trial methods and results[16]

Method of randomisation and blinding	Patients were randomised to receive either two bottles of masked brimonidine 0.02% (1 labelled morning and 1 labelled evening) or 1 bottle of masked latanoprost 0.005% (labelled evening) and 1 bottle of placebo (labelled morning). The randomisation schedule was generated by an independent pharmacist. The trial was double-blinded.
Inclusion criteria	1. Aged ≥18 years 2. Bilateral OAG or OHT 3. Had not received previous treatment with either of the study drugs. 4. The acceptable range of untreated IOP at baseline was 22-34 mmHg in both eyes. 5. Corrected visual acuity had to be ≥20/100 in each eye, and reliable visual field testing had to have been performed within the past 3 months.
Exclusion criteria	1. Significant illness that could interfere with the study measures, 2. Any contraindication to alpha-adrenergic agonist or prostaglandin therapy 3. Any ocular disease (patients with mild chronic blepharitis, age-related macular degeneration, diabetic retinopathy, or cataract could be enrolled at the discretion of the investigator), laser surgery or any other IOP procedure within 3 months of the pre-study visit 4. Planned use of ocular medications other than the study medications (except for intermittent use of "artificial tears" during the study) 5. Known hypersensitivity to the study medications or their components (benzalkonium chloride preservative) 6. A change in existing chronic therapy (whether a change in dose or discontinuation of current medication, of the additional of new medication) during the study or within 7 days before beginning the study that could significantly affect IOP 7. Corneal abnormalities that would prevent accurate IOP readings with an applanation tonometer 8. Planned use of contact lenses during the study 9. Functionally significant loss of visual field 10. Current or planned pregnancy or lactation during the study 11. Concurrent enrolment or participation in a drug study within the past 30 days.

	12. Patients were excluded or discontinued if they had or developed a condition that in the investigator's opinion put them at significant risk, had the potential to confound study results, or could interfere significantly with participation in the study
Trial setting	US (five investigational sites)
Trial drugs (intervention and comparator)	Arm 1: Brimonidine (N=64) Arm 2: Latanoprost (N=61)
Primary efficacy outcomes	• Mean IOP at baseline, month 1, and month 3 • Mean change in IOP from baseline to month 1 and month 3
Secondary efficacy outcomes	NR
Safety outcomes	Conjunctival hyperaemia, dry eye sensation, stinging or burning sensation, photophobia
Duration of follow-up	3 months

Abbreviations: IOP – Intraocular pressure; mmHg – Millimetres of mercury; NR – Not reported; OAG – Open-angle glaucoma; OHT – Ocular hypertension; US – United States

Table 73: Nixon *et al.* (2009) methods and results[10]

Method of randomisation and blinding	Patients were randomised in a 1:1 ratio by a computer generated randomisation schedule.
Inclusion criteria	1. At least 18 years old. 2. Diagnosis of OAG or OHT who were in need of lower IOP in each eye. Patients could be untreated or currently on IOP lowering therapy. The need for lower IOP was based on the opinion of the investigator.
Exclusion criteria	1. Current enrollment in a clinical trial with an investigational drug. 2. History of ophthalmic disease other than glaucoma. 3. Closed-angle glaucoma. 4. Any known contraindication to beta-blockers, alpha-agonists, or carbonic anhydrase inhibitors. 5. Asthma or chronic obstructive pulmonary disease. 6. Uncontrolled diabetes; 7. Clinically significant heart disease, second- or third-degree atrioventricular block, or sinus bradycardia. 8. Use of a monoamine oxidase inhibitor; and previous sensitivity or allergic reaction to brimonidine or dorzolamide. 9. Female patients who were pregnant, lactating, or of childbearing potential and not using reliable contraception were excluded.
Trial setting	US
Trial drugs (intervention and comparator)	Arm 1: Brimonidine/timolol (N=91)

	Arm 2: Dorzolamide/timolol (N=89)
Primary efficacy outcomes	• Mean IOP at baseline and month 3
Secondary efficacy outcomes	NR
Safety outcomes	Any treatment-emergent adverse events, conjunctivitis allergic, burning or stinging sensation, blurred vision
Duration of follow-up	3 months

Abbreviations: IOP – Intraocular pressure; NR – Not reported; OAG – Open-angle glaucoma; OHT – Ocular hypertension; US – United States

Table 74: Rigollet *et al.* (2011) methods and results[8]

Method of randomisation and blinding	Patients were assigned to medical interventions at random. Random codes were obtained by means of a computerized algorithm. The algorithm produced a block of 9 codes for patients allowing a balanced distribution 1:1:1 of study subjects to the 3 medical interventions evaluated.
Inclusion criteria	1. Age ≥18 years. 2. Primary open-angle glaucoma or ocular hypertension (IOP ≥21 mmHg at baseline) 3. Previously treated with at least 2 hypotensor drugs.
Exclusion criteria	1. Known contraindication to any of the study treatments. 2. Use of any medicine that might affect IOP. 3. Abnormal ocular condition or symptom preventing the patient from entering the study according to the investigator's judgment. 4. Pregnancy or lactancy.
Trial setting	Spain
Trial drugs (intervention and comparator)	Latanoprost/timolol (42) Bimatoprost/timolol (44) Travoprost/timolol (44)
Primary efficacy outcomes	• Absolute decrease in IOP at month 1, month 2, month 3, month 4, month 5, month 6, month 12
Secondary efficacy outcomes	NR
Safety outcomes	Dry eye sensation, eye irritation/itching/discomfort, red eye, dark eye rings
Duration of follow-up	12 months

Abbreviations: IOP – Intraocular pressure; mmHg – Millimetres of mercury; NR – Not reported

Table 75: Katz *et al.* (2013) methods and results[12]

Method of randomisation and blinding	Patients were randomized 1:1:1 to treatment with fixed-combination brinzolamide (1%) and brimonidine (0.2%); brinzolamide (1%); or brimonidine(0.2%) using an interactive web response system.
Inclusion criteria	NR
Exclusion criteria	NR

Trial setting	US
Trial drugs (intervention and comparator)	Brinzolamide/brimonidine (N=209) Brinzolamide (N=224) Brimonidine (N=216)
Primary efficacy outcomes	• Mean IOP at baseline, week 2, week 6,and month 3 (at 08:00, 10:00, 15:00, 17:00)
Secondary efficacy outcomes	NR
Safety outcomes	Any treatment-emergent adverse event, conjunctival hyperaemia, eye pruritus, punctuate keratitis, dry eye sensation, foreign body sensation, eye irritation/itching/discomfort, eye allergy, conjunctivitis, blurred vision, dysgeusia, eye pain
Duration of follow-up	3 months

Abbreviations: IOP – Intraocular pressure; NR – Not reported; US – United States

Table 76: Whitson *et al.* (2013) methods and results[13]

Method of randomisation and blinding	Patients were randomly assigned 1:1:1 to treatment with BBFC, brinzolamide 1%, or brimonidine 0.2%. Randomisation was straified by the mean baseline IOP from both eligibility visits measured at the 8 am time point (24–27 mmHg and 28–36 mmHg) to ensure balanced baseline IOP among the treatment groups.
Inclusion criteria	1. At least 18 years of age. 2. Clinical diagnosis of open-angle glaucoma or ocular hypertension in at least one (study) eye. 3. Intraocular pressure in the study eye had to be between 24 mmHg and 36 mmHg at the 8 am time point and between 21 mmHg and 36 mmHg at the 10 am time point at both eligibility visits. All IOP readings in both eyes at both eligibility visits had to be 36 mmHg or less.
Exclusion criteria	1. Any history of ocular trauma or intraocular surgery within the past six months or ocular infection, inflammation, or laser surgery within the past three months. 2. Any form of glaucoma other than open-angle glaucoma; chronic, recurrent, or severe inflammatory eye disease. 3. Central cornea thickness >620 µm in either eye. 4. Shaffer angle grade <2 in either eye. 5. Cup/disc ratio >0.80 (horizontal or vertical measurement) in either eye. 6. Severe central visual field loss in either eye, defined as sensitivity ≤10 decibels in at least two of four visual field test points closest to the point of fixation 7. Clinically significant or progressive retinal disease. 8. Corrected distance visual acuity worse than 0.6 logMAR 9. Other ocular pathology that could preclude administration of an alpha-adrenergic agonist and/or a topical carbonic anhydrase inhibitor.

	10. A recent history of taking medications prohibited during the study, including high-dose salicylate therapy within four weeks of the first eligibility visit and any medications or substances used on a chronic basis that could affect IOP and that had not been on a stable dosing regimen for at least 30 days before the screening visit. 11. Current use of any prohibited medications, including monoamine oxidase inhibitors, psychotropic drugs that augment an adrenergic response, and any additional ocular hypotensive medications. 12. History of active, severe, unstable, or uncontrolled systemic disease precluding safe administration of a topical alpha-adrenergic agonist or carbonic anhydrase inhibitor. 13. Hypersensitivity to alpha-adrenergic agonist drugs, topical or oral carbonic anhydrase inhibitors, sulfonamide derivatives, or any component of the study medications. 14. Any condition requiring treatment with glucocorticoids, unless the glucocorticoid could be safely discontinued during the study. 15. Women could not be pregnant, lactating, or of childbearing potential (unless they were abstinent or using a highly effective method of birth control).
Trial setting	US
Trial drugs (intervention and comparator)	Brinzolamide/brimonidine (N=218) Brinzolamide (N=229) Brimonidine (N=232)
Primary efficacy outcomes	• Percentage IOP reduction from baseline to 6 months • Absolute IOP reduction from baseline to 6 months
Secondary efficacy outcomes	• Mean IOP at week 2 and month 3 (at 08:00, 10:00, 15:00, 17:00)
Safety outcomes	Conjunctival hyperaemia, eye pruritus, conjunctivitis allergic, dry eye sensation, eye irritation/itching/discomfort, eye allergy, conjunctivitis, blurred vision, dysgeusia
Duration of follow-up	3 months with a 3-month safety extension

Abbreviations: IOP – Intraocular pressure; mmHg – Millimetres of mercury; USA – United States

Table 77: Kozobolis *et al.* (2017) methods and results[5]

Method of randomisation and blinding	Patients were randomly assigned into treatment groups. The trial was double-masked.
Inclusion criteria	1. Patients with newly diagnosed POAG or patients with POAG previously treated with other medications with a washout period of 1 month.
Exclusion criteria	1. Patients with previous eye operations or types of glaucoma other than POAG. 2. Age <18 years. 3. IOP>36mm at any timepoint. 4. Pregnancy. 5. Scahffer angle grade <2 (in gonioscopy)

	6. Cup-to-disc ratio >0.8. 7. Severe central visual field loss. 8. History of chronic, recurrent, or current severe inflammatory eye disease. 9. Any retinal disease. 10. Any factor that could affect compliance of the patient (illness, allergies). 11. Any β-blocker contraindication for patients of Arm 1.
Trial setting	Greece
Trial drugs (intervention and comparator)	Arm 1: Dorzolamide-timolol twice a day (N=22) Arm 2: Brinzolamide-brimonidine twice a day (N=22)
Primary efficacy outcomes	Morning IOP reduction at 12 weeks compared with baseline, mean (SD): • Dorzolamide-timolol: 7.0 (2.8) • Brinzolamide-brimonidine: 8.4 (1.9) Afternoon IOP reduction at 12 weeks compared with baseline, mean (SD): • Dozolamide-timolol: 8.6 (2.7) • Brinzolamide-brimonidine: 7.9 (1.6) Morning IOP reduction at 8 weeks compared with baseline, mean (SD): • Dorzolamide-timolol: 6.0 (2.9) • Brinzolamide-brimonidine: 8.1 (2.1) Afternoon IOP reduction at 8 weeks compared with baseline, mean (SD): • Dozolamide-timolol: 8.1 (2.9) • Brinzolamide-brimonidine: 7.9 (2.1)
Secondary efficacy outcomes	• IOP measured at 9:00 for morning IOP levels • IOP measured at 16:00 for afternoon IOP levels
Safety outcomes	Differences in conjunctival hyperaemia, ocular stinging, soreness or irritation, or foreign body sensation.
Duration of follow-up	12 weeks

Abbreviations: IOP – Intraocular pressure; NR – Not reported; OAG – Open-angle glaucoma; OHT – Ocular hypertension; POAG – Primary open-angle glaucoma; SD – Standard deviation

Table 78: MERCURY 1 methods and results[14]

Method of randomisation and blinding	Randomisation was determined by a computer generated randomization code and was stratified by site and maximum IOP (<25 vs. ≥ 25 mmHg).
Inclusion criteria	1. Must be 18 years of age or older.

	2. Diagnosis of open-angle glaucoma (OAG) or ocular hypertension (OHT) in both eyes (OAG in one eye and OHT in the fellow eye was acceptable). 3. Unmedicated (post-washout) intraocular pressure (IOP) >20 mmHg and <36 mmHg in both eyes at 2 qualification visits at 08:00 hour, 2–7 days apart. At the second qualification visit, IOP >17 mmHg and <36 mmHg. in both eyes at 10:00 and 16:00 hours. Both eyes had to have qualified at all qualification visit time points. 4. Best corrected visual acuity (BCVA) + 1.0 logMAR or better by Early Treatment Diabetic Retinopathy Study (equivalent to 20/200 or better Snellen visual acuity in each eye). 5. Be able and willing to give signed informed consent and follow study instructions.
Exclusion criteria	1. Clinically significant ocular disease which might have interfered with interpretation of the study efficacy endpoints or with safety assessments, including patients with glaucomatous damage so severe that washout of ocular hypotensive medications (if needed) for 1 month was not judged safe as it would put the patient at risk for further vision loss. 2. Pseudoexfoliation or pigment dispersion component glaucoma, history of angle closure glaucoma, or narrow angles (ie, Grade 2 or less [Shaffer scale]; extreme narrow angle with complete or partial closure). Note: Prior laser peripheral iridotomy was NOT acceptable. 3. IOP ≥36 mmHg (unmedicated) in either eye at any time point (individuals who were excluded for this criterion were not allowed to attempt requalification) or use of more than 2 ocular hypotensive medications within 30 days of screening. Note: Fixed-dose combination medications, for the purpose of this exclusion criterion, was counted as one medication. 4. Known hypersensitivity to any component of the formulation, to latanoprost, or to topical anesthetic. 5. Previous glaucoma intraocular surgery, including selective laser trabeculoplasty or argon laser trabeculoplasty in either eye. 6. Refractive surgery in either eye (eg, radial keratotomy, photorefractive keratectomy, LASIK, corneal cross-linking, etc.).

	7. Ocular trauma in either eye within the 6 months prior to screening, or ocular surgery or non-refractive laser treatment within the 3 months prior to screening. 8. Recent or current evidence of ocular infection or inflammation in either eye. Current evidence of clinically significant blepharitis, keratitis, or conjunctivitis. Additionally, current evidence or history of herpes simplex or zoster keratitis in either eye at screening was excluded. 9. Mean central corneal thickness greater than 620 µm in either eye at screening. 10. Clinically significant abnormalities in laboratory tests at screening. 11. Clinically significant systemic disease which might have interfered with the study. 12. Systemic medication that could have had a substantial effect on IOP within 30 days prior to screening, or anticipated during the study, including any corticosteroid- containing drug regardless of route of administration. 13. Women of childbearing potential who were pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. An adult woman was considered to be of childbearing potential unless she was 1 year post-menopausal or 3 months post-surgical sterilization. All females of childbearing potential had to have a negative urine pregnancy test result at the screening examination and must not 14. Have intended to become pregnant during the study.
Trial setting	Multicenter (56 active sites in 23 states across the United States)
Trial drugs (intervention and comparator)	Netarsudil/latanoprost (N=238) Netarsudil (N=244) Latanoprost (N=236)
Primary efficacy outcomes	• Mean IOP at baseline, week 2, week 6, month 3, month 9 , month 12, month 13 • Mean diurnal IOP at baseline, week 2, week 6, month 3, month 9 , month 12, month 13
Secondary efficacy outcomes	• Percentage of patients achieving prespecified thresholds for mean diurnal IOP • Mean percentage change in mean diurnal IOP
Safety outcomes	Any eye disorder, conjunctival hyperaemia, cornea verticillata, conjunctival haemorrhage, eye pruritus, punctuate keratitis, blurred vision
Duration of follow-up	12 months

Abbreviations: BCVA – Best corrected visual acuity; IOP – Intraocular pressure; mmHg – Millimetres of Mercury; OAG – Open-angle glaucoma; OHT – Ocular hypertension

Table 79: MERCURY 2 methods and results[15]

Method of randomisation and blinding	Patients were randomised (1:1:1) through an interactive web-based response system to receive once daily (PM) netarsudil 0.02%/latanoprost 0.005% FDC, once daily netarsudil 0.02%, or once daily latanoprost 0.005% for 3 months. Randomization was stratified by study site and maximum baseline IOP (<25 vs.≥25 mmHg), and the randomization code was prepared by an independent biostatistician not involved in the study's day-to-day conduct. Treatment assignments were masked to the investigator, clinical study team, and patients.
Inclusion criteria	1. Eligible participants were aged 18 years (19 years in Canada) and had an unmedicated (postwashout) IOP >20 to <36 mmHg per calibrated Goldmann applanation tonometer in both eyes at 8:00 AM at 2 qualification visits (2-7 days apart) and >17 to <36 mmHg in both eyes at 10:00 AM and 4:00 PM at the second qualification visit. 2. Patients using ocular hypotensive medications were required to undergo washout before study entry: 4 weeks for patients using prostaglandin analogs or beta-adrenoceptor antagonists before study entry, 2 weeks for those using adrenergic agonists, and 5 days for those using muscarinic agonists or carbonic anhydrase inhibitors. 3. A best corrected visual acuity of 1.0 logarithm of the minimum angle of resolution or better per Early Treatment Diabetic Retinopathy Study criteria (equivalent to 20/200 or better Snellen) measurement.
Exclusion criteria	1. An unmedicated IOP ≥36 mmHg in either eye at any time point 2. The presence of clinically significant ocular or systemic disease, pseudoexfoliation or pigment dispersion glaucoma, history of angle closure or narrow angles. 3. Use of more than 2 ocular hypotensive medications within 30 days of screening (use of an FDC product counted as 1 medication), changes in systemic medication that could have had an effect on IOP in the 30 days before screening, hypersensitivity to any component of the study drugs, previous intraocular glaucoma or refractive surgery, ocular surgery or nonrefractive laser treatment in the 3 months before screening. 4. Ocular trauma in the 6 months before screening, recent or current ocular infection or inflammation in either eye, any abnormality preventing reliable applanation tonometry of either eye, mean central

	corneal thickness >620 mm at screening (related to tonometer accuracy), and the presence of clinically significant laboratory abnormalities at screening. 5. Women of childbearing potential who were pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control were also excluded.
Trial setting	Multicenter (60 active sites in the United States and Canada)
Trial drugs (intervention and comparator)	Netarsudil/latanoprost (N=245) Netarsudil (N=255) Latanoprost (N=250)
Primary efficacy outcomes	• Mean IOP at baseline, week 2, week 6, and month 3 • Mean percentage change in IOP from baseline to week 2, week 6, and month 3
Secondary efficacy outcomes	• Percentage of patients achieving prespecified reduction in mean diurnal IOP
Safety outcomes	Any eye disorder, conjunctival hyperaemia, cornea verticillata, conjunctival haemorrhage
Duration of follow-up	3 months

Abbreviations: FDC – Fixed-dose combination; IOP – Intraocular pressure; mmHg – Millimetres of Mercury

Table 80: MERCURY 3 methods and results[6]

Method of randomisation and blinding	A randomisation code for allocating the treatments was prepared by an independent biostatistician, who was not involved in the day-to-day conduct of the study. For the duration of the study, treatment assignments were masked to the investigator, the clinical study team, Aerie/Aerie representative working on behalf of Aerie, personnel involved in day-to-day study management, (monitors, data managers, and statisticians), and the subjects.
Inclusion criteria	1. Must have been 18 years of age or older. 2. Diagnosed with of OAG or OHT in both eyes (OAG in one eye and OHT in the fellow eye was acceptable). 3. Subjects were insufficiently controlled and/or subjects were considered in need for combination therapy by the investigators. 4. Medicated IOP ≥ 17 mmHg in at least one eye and < 28mmHg in both eyes at screening visit. 5. Unmedicated (post-washout) IOP > 20mmHg in at least one eye and < 36mmHg in both eyes at 2 qualification visits at 08:00 hour, 2-7 days apart. At the second Qualification Visit, had IOP > 17mmHg in at least one eye and < 36mmHg in both eyes at 10:00 and 16:00 hours. Note: For

	purposes of determining eligibility of subjects to be enrolled, the non-integral (fractional) IOP mean number was used. Any non-integral mean (fractional) IOP number was not rounded. If only one eye qualified at the second Qualification Visit it must have been the same eye that qualified on the first visit and this was the study eye for the duration of the study. 6. Best corrected visual acuity +1.0 logarithm of the minimum angle resolvable (logMAR) or better by ETDRS in each eye (equivalent to 20/200 or better Snellen visual acuity in each eye). 7. Was able and willing to give signed informed consent and follow study instruction. 8. Women were either of non-childbearing potential, or women with child-bearing potential and men with reproductive potential were willing to practice acceptable methods of birth control during the study. 9. Women of childbearing potential had a negative urine pregnancy test within 7 days of first dose of study treatment and agreed to use highly effective contraception during the study and for 3 months after the last dose of study medication. 10. Men with a female partner of childbearing potential had either had a prior vasectomy or agreed to use an effective form of contraception from time of randomization and for 3 months following the last dose of study medication. 11. In France, a subject was eligible for inclusion in this study only if either affiliated to or as a beneficiary of a social security number
Exclusion criteria	1. Clinically significant ocular disease (e.g., corneal edema, uveitis, or severe keratoconjunctivitis sicca) which might have interfered with interpretation of the study efficacy endpoints or with safety assessments, including subjects with glaucomatous damage so severe that washout of ocular hypotensive medications for 4 weeks or longer if needed was not judged safe as it would put the subject at risk for further vision loss. 2. Pseudoexfoliation or pigment dispersion component glaucoma, history of angle closure glaucoma, or narrow angles (i.e., Grade 2 Shaffer or less extreme narrow angle with complete or partial closure). Note: Previous laser peripheral iridotomy was not acceptable. 3. Intraocular pressure ≥ 36mmHg (unmedicated) in either eye (individuals who were excluded for this criterion were not allowed to attempt requalification), or use of more than 2 ocular hypotensive

	medications within 30 days of screening. Note: FDC medications, for the purpose of this exclusion criterion, counted as one medication. However, subjects who currently took 2 FDC products were excluded. 4. Treatment-naïve subjects. 5. Prior treatment with Ganfort topical eye drops where the subjects IOP did not achieve the target IOP and was considered either a therapeutic failure or to have insufficient response. Subjects currently (immediately prior to screening visit) being treated with Ganfort were excluded from the study. 6. Known hypersensitivity to any component of the investigational formulations used (e.g., benzalkonium chloride) or to fluorescein. 7. Previous glaucoma intraocular surgery, including selective laser trabeculoplasty (SLT) or argon laser trabeculoplasty (ALT) in either eye. 8. Refractive surgery in either eye (e.g., radial keratotomy, photorefractive keratectomy (PRK), laser-assisted in situ keratomileusis (LASIK), corneal cross-linking, keratoplasty). 9. Ocular trauma within the six months prior to screening, or ocular surgery or non-refractive laser treatment within the 3 months prior to screening. 10. Recent or current evidence of ocular infection or inflammation in either eye. Current evidence of clinically significant blepharitis, conjunctivitis, keratitis, current evidence or history of herpes simplex or zoster keratitis in either eye at screening. 11. Use of ocular medication in either eye of any kind within 30 days of screening and throughout the study, with the exception of a) ocular hypotensive medications which must have been the same medication for 30 days prior to screening (which must have been washed out according to the provided schedule), b) lid scrubs (which may have been used prior to, but not after, screening), c) lubricating drops for dry eye (which could be used throughout the study), as prescribed by the investigator. 12. Mean central corneal thickness greater than 620 µm at screening.

	13. Any abnormality preventing reliable Goldmann applanation tonometry of either eye (e.g., keratoconus). 14. Clinically significant abnormalities in laboratory tests at screening. 15. Known hypersensitivity or contraindication to Ganfort and to β-adrenoceptor antagonists (e.g., chronic obstructive pulmonary disease or bronchial asthma; abnormally low blood pressure or heart rate; second or third-degree heart block or congestive heart failure, cardiac failure, cardiac shock, and severe diabetes). 16. Clinically significant systemic disease which might have interfered with the study. 17. Participation in any investigational study within 30 days prior to screening. 18. Systemic medication including corticosteroid containing drugs that could have had a substantial effect on IOP which had not been maintained at a consistent dose and regime within 30 days prior to screening and were anticipated to change in dose and/or regime during the study. 19. Use of topical steroid containing medications on the face or in or around the eyes excluded the subject. 20. Women of childbearing potential who were pregnant, nursing, planning a pregnancy, or were not using a medically acceptable and highly effective form of birth control. An adult woman was considered to be of childbearing potential unless she was one year post menopausal (1 year without menses with appropriate clinical profile, e.g., age appropriate, > 45 years in the absence of hormone replacement therapy). In questionable cases the subject must have a follicle-stimulating hormone value > 40 mIU/mL and an estradiol value < 40 pg/mL (< 140 pmol/L) or have been 3 months post-surgical sterilization. 21. Vulnerable subjects such as minors, adults under legal protection or unable to express their consent (e.g., hospitalized persons in coma), persons deprived of liberty (prisoners from jails), or persons subject to psychiatric care.
Trial setting	Multicenter (68 different sites Europe)
Trial drugs (intervention and comparator)	Netarsudil/latanoprost (N=218) Bimatoprost/timolol (N=212)
Primary efficacy outcomes	• Mean IOP at week 2, week 6, month 3 (at 08:00, 10:00, 16:00)

Secondary efficacy outcomes	• Mean diurnal IOP within a treatment group at each post-treatment visit. • Mean change from diurnally adjusted baseline IOP at each post-treatment time point. • Mean change from baseline in diurnal IOP at each post-treatment visit. • Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point. • Mean percent change from baseline in diurnal IOP at each post-treatment visit. • Percentages of subjects achieving pre-specified mean, mean change, and percent mean change in diurnal IOP levels.
Safety outcomes	Visual acuity, goniometry, pachymetry, objective biomicroscopic and ophthalmoscopic examination, and monitoring of AEs.
Duration of follow-up	6 months

Abbreviations: AE – Adverse event; ALT - Argon laser trabeculoplasty; FDC – Fixed-dose combination; IOP – Intraocular pressure; LASIK – Laser-assisted in situ keratomileusis; mmHg – Millimetres of Mercury; OAG – Open-angle glaucoma; OHT – Ocular hypertension; PRK – Photorefractive keratectomy; SLT – Selective laser trabeculoplasty

Study design of studies included in the NMA

Table 81: Comparison of study design of the studies considered for the NMA

Trial	Population	Phase	Study design	Geography
DuBiner *et al*. (2001)[16]	Patients with OAG or OHT	NR	Multicentre, double-blinded, parallel-group clinical trial	US (5 investigational sites)
Nixon *et al*. (2009)[10]	Patients with OAG or OHT in need of IOP lowering	NR	Randomised, parallel-group, observer-masked clinical trial	US
Rigollet *et al*. (2011)[8]	Patients with POAG or OHT, previously treated with at least two hypotensive drugs	NR	Randomised, prospective, single-blind study	Spain
Katz *et al*. (2013)[12]	Patients with OAG or OHT	Phase 3	Double-masked, parallel-group, multicentre study	US (66 study sites)
Whitson *et al*. (2013)[13]	Patients with OAG or OHT	Phase 3	Randomised, double-blinded, multicentre, parallel-group	US (65 study sites)
Kozobolis *et al*. (2017)[5]	Adults with newly diagnosed POAG or patients with POAG previously treated	NR	Prospective, double-masked, randomised, parallel-group study	Greece

	with other medications, with IOP ≤36mmHg			
MERCURY 1[14]	Patients with OAG and OHT with unmedicated IOP > 20 to <36 mmHg at 8:00 AM	Phase 3	Double-masked, randomised, multicentre, active-controlled, parallel-group, 12-month study,	Multicentre (56 active sites in 23 states across the US)
MERCURY 2[15]	Patients with OAG and OHT with unmedicated IOP > 20 to <36 mmHg at 8:00 AM	Phase 3	Prospective, double-masked, randomised, multicentre, active-controlled, parallel-group trial	Multicentre (60 active sites in the US and Canada)
MERCURY 3[6]	Adults diagnosed with POAG or OHT in both eyes, with medicated IOP ≥17mmHg in at least one eye and IOP <28mmHg in both eyes, and unmedicated IOP >20mmHg in at least one eye and IOP <36mmHg in both eyes at 2 eligibility visits (08:00), 2-7 days apart and IOP >17mmHg in at least one eye and IOP	Phase 3	Prospective, double-blinded, randomised, multicentre, active-controlled, parallel-group	Austria, Belgium, Czechia, France, Germany, Hungary, Italy, Latvia, Poland, Spain, UK

	<36mmHg in both eyes at 10:00 and 16:00 at second qualification visit.			

Abbreviations: IOP – Intraocular pressure; mmHg – Millimetres of Mercury; NMA – Network meta-analysis; NR – Not reported; OAG – Open-angle glaucoma; OHT – Ocular hypertension; POAG – Primary open-angle glaucoma; UK – United Kingdom; US – United States

Table 82: Comparison of study design of the studies considered for the NMA (continued)

Trial	Intervention(s)	Randomisation	Randomisation method	Blinding	Follow-up duration
DuBiner *et al*. (2001)[16]	Treatment arm 1: Brimonidine 0.2% Treatment arm 2: Latanoprost 0.005%	At the baseline visit, patients were randomised to receive brimonidine 0.2% or latanoprost 0.005%.	Patients were randomised to receive either two bottles of masked brimonidine 0.02% (1 labelled morning and 1 labelled evening) or 1 bottle of masked latanoprost 0.005% (labelled evening) and 1 bottle of placebo (labelled morning). Randomisation schedule was generated by an independent pharmacist.	Double-blinded	3 months
Nixon *et al*. (2009)[10]	Treatment arm 1: Brimonidine 0.2% /timolol 0.5%	Patients were randomised in a 1:1 ratio to receive brimonidine 0.2%/timolol	Computer generated randomisation schedule	Observer-masked	3 months

	Treatment arm 2: Dorzolamide 2%/ timolol 0.5%	0.5% or dorzolamide 2% /timolol 0.5%			
Rigollet *et al*. (2011)[8]	Treatment arm 1: Latanoprost 50ug /timolol 5mg/1ml Treatment arm 2: Travoprost 40 ug/ timolol 5mg/1ml Treatment arm 3: Bimatoprost 300ug/timolol 5mg/1 ml	Patients were randomised in a 1:1:1 ratio to the three medical interventions evaluated.	Computer generated randomisation schedule	Single-blinded	12 months
Katz *et al*. (2013)[12]	Treatment arm 1: Brinzolamide 1.0%/ brimonidine 0.2% Treatment arm 2: Brinzolamide 1.0% Treatment arm 3: Brimonidine 0.2%	Patients were randomized 1:1:1 to treatment with fixed-combination brinzolamide (1%) and brimonidine (0.2%); brinzolamide (1%); or brimonidine(0.2%)	Interactive web response system	Double-blinded	3 months

Whitson *et al*. (2013)[13]	Treatment arm 1: Brinzolamide 1.0%/ brimonidine 0.2% Treatment arm 2: Brinzolamide 1.0% Treatment arm 3: Brimonidine 0.2%	Patients were randomly assigned 1:1:1 to treatment with brinzolamide/brimonidine, brinzolamide 1%, or brimonidine 0.2%. Randomisation was stratified by the mean baseline IOP from both eligibility visits measured at the 8 am time point (24–27 mmHg and 28–36 mmHg) to ensure balanced baseline IOP among the treatment groups.	NR	Double-blinded	3 months + 3 months safety extension
Kozobolis *et al*. (2017)[5]	Treatment arm 1: Dorzolamide 2%/timolol 0.5% Treatment arm 2: Brinzolamide/ brimonidine	Patients were randomly assigned to receive dorzolamide/timolol or brinzolamide/brimonidine.	NR	Double-blinded	3 months

MERCURY 1[14]	Treatment arm 1: Netarsudil 0.02%/ latanoprost 0.005% Treatment arm 2: Netarsudil 0.02% Treatment arm 3: Latanoprost 0.005%	Randomization was stratified by site and maximum IOP (<25 vs. ≥ 25 mmHg).	Computer generated randomisation	Double-blinded	12 months
MERCURY 2[15]	Treatment arm 1: Netarsudil 0.02%/ latanoprost 0.005% Treatment arm 2: Netarsudil 0.02% Treatment arm 3: Latanoprost 0.005%	Patients were randomized 1:1:1 to receive once daily (PM) netarsudil 0.02%/latanoprost 0.005% FDC, once daily netarsudil 0.02%, or once daily latanoprost 0.005% for 3 months. Randomisation was stratified by study site and maximum baseline IOP (<25 vs.≥25 mmHg)	Investigator generated code randomisation	Double-blinded	3 months
MERCURY 3[6]	Treatment arm 1: Netarsudil 0.02% /Latanoprost 0.005%	Patients were randomised in a 1:1 ratio to receive netarsudil-latanoprost or bimatoprost-timolol. Randomisation was	Randomisation code prepared by an independent biostatistician	Double-blinded	6 months

	Treatment arm 2: Bimatoprost 0.03%/ timolol 0.5%	stratified by investigative site and maximum baseline IOP < 25mmHg vs. ≥ 25mmHg			

Abbreviations: FDC – Fixed-dose combination; IOP – Intraocular pressure; mmHg – Millimetres of mercury; NMA – Network meta-analysis; NR – Not reported

Baseline characteristics of studies included in the NMA

Table 83: Comparison of baseline characteristics in the studies considered for the NMA

Trial	Treatment arm (sample size)	Mean age (years) (SD)	IOP at screening – study eye (mmHg), mean (SD)	Mean diurnal IOP (mmHg) at baseline, mean (SD)	Visual field mean deviation (dB), mean ± SD	Corneal thickness (µm), mean ± SD	Family history of glaucoma
DuBiner *et al*. (2001)[16]	Brimonidine (66)	Mean (range): 61 (37-86)	NR	All patients: 24.5 (2.2) Treatment-naïve patients: 24.0 (1.8) Previously treated patients: 24.8 (2.5)	NR	NR	NR
	Latanoprost (61)	Mean (range): 61 (39-84)	NR	All patients: 24.1 (1.9) Treatment-naïve patients: 23.8 (1.4)	NR	NR	NR

				Previously treated patients: 24.4 (2.3)			
Nixon *et al*. (2009)[10]	Brimonidine-timolol (91)	67.5 (12.4)	23.0 (4.4)	NR	NR	NR	NR
	Dorzolamide-timolol (89)	68.0 (11.4)	23.6 (4.5)	NR	NR	NR	NR
Rigollet *et al*. (2011)[8]	Latanoprost-timolol (42)	NR	NR	27.6 (NR)	NR	NR	NR
	Bimatoprost-timolol (42)	65.74 (NR)	NR	28.0 (NR)	NR	NR	NR
	Travoprost-timolol (44)	70.95 (NR)	NR	26.4 (NR)	NR	NR	NR
Katz *et al*. (2013)[12]	Brinzolamide-brimonidine (209)	63.9 (11.3)	Baseline, 8 AM: 26.9 (2.6) Baseline, 10 AM: 25.3 (2.8) Baseline, 3 PM: 23.7 (3.0) Baseline, 5 PM: 23.2 (3.1)	NR	NR	NR	NR
	Brinzolamide (224)	65.0 (10.0)	Baseline, 8 AM: 27.1 (2.6) Baseline, 10 AM: 25.4 (2.7) Baseline, 3 PM: 23.8 (3.2) Baseline, 5 PM: 23.6 (3.4)	NR	NR	NR	NR

	Brimonidine (216)	64.3 (10.8)	Baseline, 8 AM: 27.0 (2.6) Baseline, 10 AM: 25.4 (2.8) Baseline, 3 PM: 24.0 (3.3) Baseline, 5 PM: 23.7 (3.3)	NR	NR	NR	NR
Whitson *et al*. (2013)[13]	Brinzolamide-brimonidine (218)	65.7 (10.3)	NR	8AM: 27.2 (2.8) 10AM: 25.8 (3.1) 3PM: 24.4 (3.7) 5PM: 24.1 (3.7)	NR	NR	NR
	Brinzolamide (229)	64.2 (10.3)	NR	8AM: 27.2 (2.7) 10AM: 26.0 (3.2) 3PM: 24.4 (3.6) 5PM: 24.2 (3.9)	NR	NR	NR
	Brimonidine (232)	64.9 (10.5)	NR	8AM: 27.3 (2.7) 10AM: 25.8 (3.0) 3PM: 24.0 (3.4) 5PM: 23.7 (3.6)	NR	NR	NR
Kozobolis *et al*. (2017)[5]	Brinzolamide-brimonidine (22)	65.2 (7.9)	NR	Morning: 28.0 ± 2.4 Afternoon: 28.2 ± 2.5	NR	NR	NR
	Dorzolamide-timolol (22)	65.3 (6.5)	NR	Morning: 28.6 ± 1.8 Afternoon: 28.4 ± 2.0	NR	NR	NR
MERCURY 1[14]	Netarsudil-latanoprost (238)	64.4 (11.33)	NR	23.7 (NR)	NR	NR	NR
	Latanoprost (236)	65.4 (10.98)	NR	23.5 (NR)	NR	NR	NR

MERCURY 2[15]	Netarsudil-latanoprost (245)	64.2 (11.81)	NR	23.5 (NR)	NR	NR	NR
	Latanoprost (250)	64.3 (11.41)	NR	23.5 (NR)	NR	NR	NR
MERCURY 3[6]	Netarsudil-latanoprost (n=218)	67.3 (12.03)	20.567 (2.3931)	Day 1: 25.054 (3.4051)	-1.670 (4.2439)	547.67 (32.455)	NR
	Bimatoprost-timolol (n=212)	67.0 (11.27)	20.4843(2.4443)	Day 1: 24.814 (3.2555) Week 2: 15.56(0.18)	-2.009 (4.3564)	550.59 (34.510)	NR

Abbreviations: dB – Decibels; IOP – Intraocular pressure; mmHg – Millimetres of mercury; NMA – Network meta-analysis; NR – Not reported; SD – Standard deviation

Table 84: Comparison of baseline characteristics in the studies considered for the NMA (continued)

Trial	Treatment arm (sample size)	Cup-to-disc ratio, mean ± SD	Disc haemorrhages	Baseline visual field indices	Retinal nerve fibre layer	Corneal hysteresis	Previous treatment[a]
DuBiner *et al*. (2001)[16]	Brimonidine (64)	NR	NR	NR	NR	NR	Ocular hypotensive treatment status, n (%) Treatment naïve: 26 (39.4) Previously treated: 40 (60.6) Of those previously treated, taking stable beta-blocker therapy: 34/40 (85)

	Latanoprost (61)	NR	NR	NR	NR	NR	Ocular hypotensive treatment status, n (%) Treatment naïve: 29 (47.5) Previously treated: 32 (52.5) Of those previously treated, taking stable beta-blocker therapy: 29/32 (91)
Nixon *et al*. (2009)[10]	Brimonidine-timolol (91)	NR	NR	NR	NR	NR	Ongoing PGA treatment Yes: 37 (41) Bimatoprost: 12 (13) Latanoprost: 17 (19) Travoprost: 8 (9) No: 54 (59)
	Dorzolamide-timolol (89)	NR	NR	NR	NR	NR	Ongoing PGA treatment Yes: 42 (47) Bimatoprost: 9 (10) Latanoprost: 22 (25) Travoprost: 11 (12) No: 47 (53)
Rigollet *et al*. (2011)[8]	Latanoprost-timolol (42)	NR	NR	NR	NR	NR	NR

	Bimatoprost-timolol (42)	NR	NR	NR	NR	NR	NR
	Travoprost-timolol (44)	NR	NR	NR	NR	NR	NR
Katz *et al*. (2013)[12]	Brinzolamide-brimonidine (209)	NR	NR	NR	NR	NR	NR
	Brinzolamide (224)	NR	NR	NR	NR	NR	NR
	Brimonidine (216)	NR	NR	NR	NR	NR	NR
Whitson *et al*. (2013)[13]	Brinzolamide-brimonidine (218)	NR	NR	NR	NR	NR	NR
	Brinzolamide (229)	NR	NR	NR	NR	NR	NR
	Brimonidine (232)	NR	NR	NR	NR	NR	NR
Kozobolis *et al*. (2017)[5]	Brinzolamide-brimonidine (22)	NR	NR	NR	NR	NR	Other medications Naïve: 45.5% Washout: 54.5%
	Dorzolamide-timolol (22)	NR	NR	NR	NR	NR	Other medications Naïve: 40.9% Washout: 59.1%
MERCURY 1[14]	Netarsudil-latanoprost (238)	NR	NR	NR	NR	NR	Combination therapy: 31 (13.0)

							Prostaglandins (monotherapy): 134 (56.3) Other (monotherapy): 19 (8.0) No prior therapy: 54 (22.7) Previously undergone prostaglandin hypotensive therapy, Yes: 162 (68.1) Previously undergone prostaglandin hypotensive therapy, No: 76 (31.9)
	Latanoprost (236)	NR	NR	NR	NR	NR	Combination therapy: 23 (9.7) Prostaglandins (monotherapy): 125 (53.0) Other (monotherapy): 19 (8.1) No prior therapy: 69 (29.2) Previously undergone prostaglandin hypotensive therapy, Yes: 144 (61.0)

							Previously undergone prostaglandin hypotensive therapy, No: 92 (39.0)
MERCURY 2[15]	Netarsudil-latanoprost (245)	NR	NR	NR	NR	NR	Combination therapy: 24 (9.8) Prostaglandin monotherapy: 119 (48.6) Other monotherapy: 16 (6.5) No prior therapy: 86 (35.1)
	Latanoprost (250)	NR	NR	NR	NR	NR	Combination therapy: 30 (12.0) Prostaglandin monotherapy: 112 (44.8) Other monotherapy: 25 (10.0) No prior therapy: 83 (33.2)
MERCURY 3[6]	Netarsudil-latanoprost (n=218)	[redacted]	NR	NR	NR	NR	Prior combination, PGA, or other monotherapies: 100% Prior PGA therapy Yes: 78.4% No: 21.6%

	Bimatoprost-timolol (n=212)	[redacted]	NR	NR	NR	NR	Prior combination, PGA, or other monotherapies: 100% Prior PGA therapy Yes: 69.3% No: 30.7%

Abbreviations: NMA – Network meta-analysis; NR – Not reported; PGA – Prostaglandin analogue; SD – Standard deviation

[a]Previous treatment was not deemed to be a key prognostic variable or treatment effect modifier; previous treatment is included in baseline characteristics comparison to assess the implications of varying study eligibility criteria between the network.

Appendix C

Wastage full values

Table 85: Netarsudil-latanoprost wastage (values from CEM)

Intervention	Pack size (ml or tablet)	Shelf life, cycles	Drops administered per cycle	Drops per pack	% of product wasted per month	No wastage: Cost per drop/tablet (£)	Wastage: Cost per drop/tablet (£)
Netarsudil-latanoprost	2.50	1	60.88	71.43	22%	£0.20	0.24

Abbreviations: CEM – Cost-effectiveness model; ml – Millilitres

Table 86: Comparator wastage (values from CEM)

Active ingredient	Product name (if not generic)	Product specific	Expiry-life, cycles (sourced from SmPC)	Drops administered per cycle	Drops per pack	% of product wasted per cycle	Wastage: Price per drop/unit (£)	Live: Price per drop/unit (£)
BRINZOLAMIDE & TIMOLOL	AZARGA	AZARGAEYEDR5/10 MG5ML	1	121.75	100.00	0%	0.11	0.11
	Generic	TIMOLOL/BRINZOLA MIEYEDR5/10MG5ML		121.75	100.00	0%	0.03	0.03
DORZOLAMIDE & TIMOLOL	Generic	DORZOLAMID/TIMOL OLEYEDROPS2%60. 2ML	1	NA	NA	NA	0.30	0.30
	Generic	DORZOL/TIMOLOLSD ZEYEDROPS5ML		121.75	100.00	0%	0.02	0.02
	Generic	DORZOL/TIMOLOL ZVA EYEDROPS5ML		121.75	100.00	0%	0.02	0.02
	Generic	DORZOLAMID/TIMOL OLEYEDROPS5ML		121.75	100.00	0%	0.02	0.02
	COSOPT	COSOPTEYEDROPS 5ML		121.75	100.00	0%	0.10	0.10

	COSOPT	COSOPTMSDEYEDROPS5ML		121.75	100.00	0%	0.10	0.10
	COSOPT	COSOPTEYEDROPU/D60.2ML		NA	NA	NA	0.48	0.48
		Placeholder for PI						
	COSOPT	COSOPTIMULTIEYEDROPS10ML		121.75	200.00	0%	0.14	0.14
	EYELAMDO	EYLAMDOPFEYEDROPS5ML		121.75	100.00	0%	0.08	0.08
	VIZIDOR	VIZIDORDUOPFEYEDROPS5ML		121.75	100.00	0%	0.08	0.08
LATANOPROST & TIMOLOL	Generic	LATANOPROST/TIMOLEYEDROPS2.5ML	1	60.88	50.00	0%	0.10	0.10
	Generic	LATANOPROST/TIZVAEYEDROPS2.5ML		60.88	50.00	0%	0.10	0.10
	Generic	LATANOPRST/TIMSDZEYEDROPS2.5ML		60.88	50.00	0%	0.10	0.10

	FIXAPOST	FIXAPOSTPFE/DUDV 30.2ML		NA	NA	NA	0.45	0.45
	MEDOX	MEDOX50MCG/5MG/ ML2.5ML		60.88	50.00	0%	0.28	0.28
	XALACOM	XALACOMEYEDROP S2.5ML		60.88	50.00	0%	0.29	0.29
TAFLUPROST & TIMOLOL	Taptiqom	TAPTIQOME/D15Y&5 MG30.3ML	3	NA	NA	NA	0.48	0.48
BIMATOPROST & TIMOLOL	Generic	BIMATOPRO/TIMOZV AEYEDROPS3ML	1	60.88	60.00	7%	0.25	0.25
	Generic	BIMATOPROST/TIMO LOEYEDROPS3ML		60.88	60.00	7%	0.25	0.25
	EYZEETAN	EYZEETANEYEDROP S3ML		60.88	60.00	7%	0.25	0.25
	GANFORT	GANFORTEYEDROP S33ML		60.88	60.00	7%	0.25	0.25
	GANFORT	GANFORTEYEDROP S3ML		60.88	60.00	7%	0.25	0.25

	GANFORT	GANFORTVIALSU/D3 0.4ML		NA	NA	NA	0.60	0.60
TRAVOPROST & TIMOLOL	Generic	TRAVOPROSTTIMOL OLEYE/DROPSOL2.5 ML	1	60.88	50.00	0%	0.09	0.09
	DUOTRAV	DUOTRAVEYE/DROP SOL2.5ML		60.88	50.00	0%	0.28	0.28
Brinzolamide and brimonidine	SIMBRINZA	Simbrinza 10mg/ml / 2mg/ml eye drops	1	121.75	100.00	0%	0.09	0.09
BRIMONIDINE & TIMOLOL	COMBIGAN	COMBIGANEYEDRO PS35ML	1	121.75	100.00	0%	0.27	0.27
	COMBIGAN	COMBIGANEYEDRO PS5ML		121.75	100.00	0%	0.10	0.10

Appendix D

Resubmission of cost-effectiveness results

Summary of base case analysis inputs

Table 87: Summary of variables applied in the base case economic analysis

Variable	Value	OWSA			Within PSA varied by	Reference to section in submission
		SE	Lower bound	Upper bound		
Model settings						
Cohort size	1,000	-	-	-	-	-
Time horizon	33 years	-	-	-	-	B.3.2.2
Total number of cycles	394	-	-	-	-	B.3.2.2
Age	67.20 years	11.65	46.34	91.88	Gamma	B.3.2.2
Percentage male	48.10%	0.10	29.55%	66.93%	Beta	B.3.2.2
Discount rate costs	3.5%	-	-	-	-	B.3.2.2
Discount rate outcomes	3.5%	-	-	-	-	B.3.2.2
Drug acquisition costs						
Years of blended market share post discontinuation	16.40	3.28	10.61	23.43	Gamma	Question B17 response
LiGHT multiplier - <20% reduction in IOP	1.05	-	-	-	-	
LiGHT multiplier - 20% - 30% reduction in IOP	1.025	-	-	-	-	
LiGHT multiplier - >30% reduction in IOP	1	-	-	-	-	
Netarsudil-latanoprost acquisition cost per cycle	£14.51	2.90	9.39	20.72	Gamma	B.3.5.1
Brinzolamide-timolol acquisition cost per cycle	£7.34	1.47	4.75	10.48	Gamma	

Variable	Value	OWSA			Within PSA varied by	Reference to section in submission
		SE	Lower bound	Upper bound		
Dorzolamide-timolol acquisition cost per cycle	£9.56	1.91	6.19	13.65	Gamma	
Latanoprost-timolol acquisition cost per cycle	£12.22	2.44	7.91	17.45	Gamma	
Bimatoprost-timolol acquisition cost per cycle	£15.82	3.16	10.24	22.60	Gamma	
Brimonidine-timolol acquisition cost per cycle	£13.74	2.75	8.89	19.63	Gamma	
Travoprost-timolol acquisition cost per cycle	£12.18	2.44	7.88	17.40	Gamma	
Tafluprost-timolol acquisition cost per cycle	£14.71	2.94	9.52	21.01	Gamma	
Brinzolamide-brimonidine acquisition cost per cycle	£11.24	2.25	7.27	16.05	Gamma	
Second line costs						
Netarsudil-latanoprost acquisition cost per cycle	£14.77	2.90	9.56	21.10	Gamma	Question B7 response
Brinzolamide-timolol acquisition cost per cycle	£7.34	1.47	9.59	21.16	Gamma	
Dorzolamide-timolol acquisition cost per cycle	£14.85	2.97	9.61	21.22	Gamma	
Latanoprost-timolol acquisition cost per cycle	£15.25	3.05	9.87	21.78	Gamma	
Bimatoprost-timolol acquisition cost per cycle	£8.30	1.66	5.37	11.86	Gamma	
Brimonidine-timolol acquisition cost per cycle	£13.74	2.75	9.54	21.06	Gamma	
Travoprost-timolol acquisition cost per cycle	£14.77	2.95	9.56	21.10	Gamma	
Tafluprost-timolol acquisition cost per cycle	£14.76	2.95	9.55	21.08	Gamma	

Variable	Value	OWSA			Within PSA varied by	Reference to section in submission
		SE	Lower bound	Upper bound		
Brinzolamide-brimonidine acquisition cost per cycle	£14.79	2.96	9.57	21.13	Gamma	
Drug administration costs						
Netarsudil-latanoprost administration cost per cycle	£0.00	0.00	0.00	0.00	Gamma	B.3.5.1
Brinzolamide-timolol administration cost per cycle	£0.00	0.00	0.00	0.00	Gamma	
Dorzolamide-timolol administration cost per cycle	£0.00	0.00	0.00	0.00	Gamma	
Latanoprost-timolol administration cost per cycle	£0.00	0.00	0.00	0.00	Gamma	
Bimatoprost-timolol administration cost per cycle	£0.00	0.00	0.00	0.00	Gamma	
Brimonidine-timolol administration cost per cycle	£0.00	0.00	0.00	0.00	Gamma	
Travoprost-timolol administration cost per cycle	£0.00	0.00	0.00	0.00	Gamma	
Tafluprost-timolol administration cost per cycle	£0.00	0.00	0.00	0.00	Gamma	
Brinzolamide-brimonidine administration cost per cycle	£0.00	0.00	0.00	0.00	Gamma	
Concomitant therapies						
SLT unit cost	£167.10	33.42	108.14	238.68	Gamma	B.3.5.4
Trabeculectomy unit cost	£1769.79	353.96	1,145.32	2,527.98	Gamma	
Proportion of patients with add-on SLT: <20% reduction in IOP	0.29%	0.00%	0.00%	1.00%	Beta	
Proportion of patients with add-on SLT: 20% - 30% reduction in IOP	0.26%	0.00%	0.00%	1.00%	Beta	
Proportion of patients with add-on SLT: >30% reduction in IOP	0.24%	0.00%	0.00%	0.00%	Beta	

Variable	Value	OWSA			Within PSA varied by	Reference to section in submission
		SE	Lower bound	Upper bound		
Proportion of patients with add-on trabeculectomy: <20% reduction in IOP	1.88%	0.00%	1.00%	2.00%	Beta	
Proportion of patients with add-on trabeculectomy: 20% - 30% reduction in IOP	1.71%	0.00%	1.00%	2.00%	Beta	
Proportion of patients with add-on trabeculectomy: >30% reduction in IOP	1.57%	0.00%	1.00%	2.00%	Beta	
<20% reduction in IOP total cost	39.58	7.92	25.61	56.54	Gamma	B.3.4.6
20% - 30% reduction in IOP total cost	38.64	7.73	25.00	55.19	Gamma	
>30% reduction in IOP total cost	37.70	7.54	24.39	53.84	Gamma	
Netarsudil-latanoprost adverse event total cost (cycle 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Netarsudil-latanoprost adverse event total cost (cycle 2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Netarsudil-latanoprost adverse event total cost (cycle 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Netarsudil-latanoprost adverse event total cost (cycle 4+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Brinzolamide-timolol adverse event total cost (cycle 1)	33.40	6.68	21.62	47.71	Gamma	
Brinzolamide-timolol adverse event total cost (cycle 2)	30.44	6.09	19.70	43.49	Gamma	
Brinzolamide-timolol adverse event total cost (cycle 3)	21.50	4.30	13.91	30.71	Gamma	
Brinzolamide-timolol adverse event total cost (cycle 4+)	0.00	0.00	0.00	0.00	Gamma	
Dorzolamide-timolol adverse event total cost (cycle 1)	42.93	8.59	27.78	61.33	Gamma	

Variable	Value	OWSA			Within PSA varied by	Reference to section in submission
		SE	Lower bound	Upper bound		
Dorzolamide-timolol adverse event total cost (cycle 2)	39.97	7.99	25.87	57.10	Gamma	
Dorzolamide-timolol adverse event total cost (cycle 3)	29.88	5.98	19.33	42.67	Gamma	
Dorzolamide-timolol adverse event total cost (cycle 4+)	0.01	0.00	0.00	0.01	Gamma	
Latanoprost-timolol adverse event total cost (cycle 1)	32.04	6.41	20.74	45.77	Gamma	
Latanoprost-timolol adverse event total cost (cycle 2)	31.92	6.38	20.66	45.60	Gamma	
Latanoprost-timolol adverse event total cost (cycle 3)	23.81	4.76	15.41	34.01	Gamma	
Latanoprost-timolol adverse event total cost (cycle 4+)	5.42	1.08	3.51	7.74	Gamma	
Tafluprost-timolol adverse event total cost (cycle 1)	38.43	7.69	24.87	54.90	Gamma	
Tafluprost-timolol adverse event total cost (cycle 2)	37.67	7.53	24.38	53.81	Gamma	
Tafluprost-timolol adverse event total cost (cycle 3)	24.10	4.82	15.60	34.42	Gamma	
Tafluprost-timolol adverse event total cost (cycle 4+)	5.41	1.08	3.50	7.73	Gamma	
Bimatoprost-timolol adverse event total cost (cycle 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Bimatoprost-timolol adverse event total cost (cycle 2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Bimatoprost-timolol adverse event total cost (cycle 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Bimatoprost-timolol adverse event total cost (cycle 4+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Brimonidine-timolol adverse event total cost (cycle 1)	56.62	11.32	36.64	80.88	Gamma	

Variable	Value	OWSA			Within PSA varied by	Reference to section in submission
		SE	Lower bound	Upper bound		
Brimonidine-timolol adverse event total cost (cycle 2)	48.36	9.67	31.29	69.07	Gamma	
Brimonidine-timolol adverse event total cost (cycle 3)	26.45	5.29	17.12	37.79	Gamma	
Brimonidine-timolol adverse event total cost (cycle 4+)	0.01	0.00	0.00	0.01	Gamma	
Travoprost-timolol adverse event total cost (cycle 1)	36.26	7.25	23.47	51.80	Gamma	
Travoprost-timolol adverse event total cost (cycle 2)	35.50	7.10	22.97	50.71	Gamma	
Travoprost-timolol adverse event total cost (cycle 3)	19.21	3.84	12.43	27.44	Gamma	
Travoprost-timolol adverse event total cost (cycle 4+)	5.42	1.08	3.51	7.74	Gamma	
Brinzolamide-brimonidine adverse event total cost (cycle 1)	43.93	8.79	28.43	62.74	Gamma	
Brinzolamide-brimonidine adverse event total cost (cycle 2)	35.66	7.13	23.08	50.94	Gamma	
Brinzolamide-brimonidine adverse event total cost (cycle 3)	15.53	3.11	10.05	22.19	Gamma	
Brinzolamide-brimonidine adverse event total cost (cycle 4+)	0.00	0.00	0.00	0.00	Gamma	
Utility inputs						
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	B.3.4.6
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Netarsudil-latanoprost adverse event total disutility (cycle 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Netarsudil-latanoprost adverse event total disutility (cycle 2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Variable	Value	OWSA			Within PSA varied by	Reference to section in submission
		SE	Lower bound	Upper bound		
Netarsudil-latanoprost adverse event total disutility (cycle 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Netarsudil-latanoprost adverse event total disutility (cycle 4+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Brinzolamide-timolol adverse event total disutility (cycle 1)	0.01	0.00	0.00	0.01	Beta	
Brinzolamide-timolol adverse event total disutility (cycle 2)	0.00	0.00	0.00	0.00	Beta	
Brinzolamide-timolol adverse event total disutility (cycle 3)	0.00	0.00	0.00	0.00	Beta	
Brinzolamide-timolol adverse event total disutility (cycle 4+)	0.00	0.00	0.00	0.00	Beta	
Dorzolamide-timolol adverse event total disutility (cycle 1)	0.01	0.00	0.01	0.01	Beta	
Dorzolamide-timolol adverse event total disutility (cycle 2)	0.01	0.00	0.00	0.01	Beta	
Dorzolamide-timolol adverse event total disutility (cycle 3)	0.00	0.00	0.00	0.01	Beta	
Dorzolamide-timolol adverse event total disutility (cycle 4+)	0.00	0.00	0.00	0.00	Beta	
Latanoprost-timolol adverse event total disutility (cycle 1)	0.01	0.00	0.00	0.01	Beta	
Latanoprost-timolol adverse event total disutility (cycle 2)	0.01	0.00	0.00	0.01	Beta	
Latanoprost-timolol adverse event total disutility (cycle 3)	0.00	0.00	0.00	0.00	Beta	
Latanoprost-timolol adverse event total disutility (cycle 4+)	0.00	0.00	0.00	0.00	Beta	
Tafluprost-timolol adverse event total disutility (cycle 1)	0.01	0.00	0.00	0.01	Beta	
Tafluprost-timolol adverse event total disutility (cycle 2)	0.00	0.00	0.00	0.01	Beta	

Variable	Value	OWSA			Within PSA varied by	Reference to section in submission
		SE	Lower bound	Upper bound		
Tafluprost-timolol adverse event total disutility (cycle 3)	0.00	0.00	0.00	0.00	Beta	
Tafluprost-timolol adverse event total disutility (cycle 4+)	0.00	0.00	0.00	0.00	Beta	
Bimatoprost-timolol adverse event total disutility (cycle 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Bimatoprost-timolol adverse event total disutility (cycle 2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Bimatoprost-timolol adverse event total disutility (cycle 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Bimatoprost-timolol adverse event total disutility (cycle 4+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Brimonidine-timolol adverse event total disutility (cycle 1)	0.01	0.00	0.01	0.02	Beta	
Brimonidine-timolol adverse event total disutility (cycle 2)	0.01	0.00	0.00	0.01	Beta	
Brimonidine-timolol adverse event total disutility (cycle 3)	0.00	0.00	0.00	0.01	Beta	
Brimonidine-timolol adverse event total disutility (cycle 4+)	0.00	0.00	0.00	0.00	Beta	
Travoprost-timolol adverse event total disutility (cycle 1)	0.01	0.00	0.01	0.02	Beta	
Travoprost-timolol adverse event total disutility (cycle 2)	0.01	0.00	0.00	0.01	Beta	
Travoprost-timolol adverse event total disutility (cycle 3)	0.00	0.00	0.00	0.01	Beta	
Travoprost-timolol adverse event total disutility (cycle 4+)	0.00	0.00	0.00	0.00	Beta	
Brinzolamide-brimonidine adverse event total disutility (cycle 1)	0.01	0.00	0.00	0.01	Beta	
Brinzolamide-brimonidine adverse event total disutility (cycle 2)	0.00	0.00	0.00	0.00	Beta	

Variable	Value	OWSA			Within PSA varied by	Reference to section in submission
		SE	Lower bound	Upper bound		
Brinzolamide-brimonidine adverse event total disutility (cycle 3)	0.00	0.00	0.00	0.00	Beta	
Brinzolamide-brimonidine adverse event total disutility (cycle 4+)	0.00	0.00	0.00	0.00	Beta	

Abbreviations: IOP – Intraocular pressure; OWSA – One-way sensitivity analysis; PSA – Probability sensitivity analysis; SE – Standard error; SLT – Selective laser trabeculoplasty

Assumptions

Table 88 details the assumptions that underpin the resubmitted cost-effectiveness model.

Table 88: Assumptions underpinning cost-effectiveness model

Factor	Assumed values	Justification
Time horizon	Lifetime (33 years)	NICE guidelines state that a time horizon must be long enough to capture differences in costs and health outcomes.[102] The mean age of patients in the MERCURY 3 trial is 67.2 years. Therefore a lifetime time horizon of 33 years is suitable to capture outcomes, as it is assumed that all patients will be dead by the age of 100 in accordance with standard modelling practice.[6] A lifetime time horizon was also used in existing models in the published literature (NICE guidelines 2017[103], Gazzard 2019[88]).
Cycle length	1-month (30.44 days)	This aligns with the MERCURY 3 trial, in which IOP was generally measured at monthly intervals. Using a 1-month cycle length allows for optimal granularity in model inputs and enables reflection of rapid reductions in IOP from baseline, as observed in the MERCURY 3 trial.
Half-cycle correction applied	Included in base case	A half-cycle correction was applied to costs and health outcomes in the Markov model to align with conventional modelling standards.
Health states	• <20% reduction in IOP from baseline • 20-30% reduction in IOP from baseline • >30% reduction in IOP from baseline • Death	IOP was deemed the most suitable outcome from which to define health states reflective of the long-term goals of POAG and OHT treatment. Clinically applicable target IOP ranges vary from patient to patient, dependent on the severity of their glaucoma. As such, defining health states based on absolute IOP thresholds was deemed unsuitable for this analysis. The structure of the economic model was designed to capture benefits in reductions in disease progression, and therefore higher QoL and lower costs associated, using health states defined by percentage change from baseline in IOP.

Factor	Assumed values	Justification
		The IOP reduction thresholds of <20%, 20-30%, and >30% were applied in the model based on published sources which applied 20% and 30% IOP reduction thresholds as indicators of treatment success, preventing progression, and a typical treatment target.[59,60,88,104] The thresholds further align with the suggested upper limit of initial target IOP for each eye, as per the Canadian Ophthalmological Society evidence-based clinical practice guidelines for glaucoma management.[38] Prior to model development, the proposed health states were validated with a UK clinical expert who confirmed the health state approach (IOP reduction from baseline) and thresholds were appropriate for patients with POAG and OHT.[32]
Model approach	Markov state transition cohort model	Treatment effectiveness is captured by distinct IOP reduction categories (<20%, 20-30%, >30%), which map to resource use, costs, and patient quality-of-life. Therefore, a Markov state transition cohort structure is appropriate to capture sustained response to treatment.
Background mortality	Background mortality data based on national life tables was applied in the model, with POAG and OHT considered to have no impact on mortality risk	In the economic model, only general background population mortality is applied; it is assumed that mortality is unaffected by POAG or OHT diagnosis and IOP percentage reduction. This methodology is in line with the NG81 cost-effectiveness model where throughout the model, individuals had a probability of dying which was age-dependent and independent from the stage of OHT or POAG.[33] This approach was also validated by a UK clinical expert.[105]
Baseline age	67.2 years	The mean age at which patients enter the model is informed by the ITT population in MERCURY 3.[6]
Proportion of males	48.1%	The proportion of males in the model is informed by the ITT population in MERCURY 3.[6]
Resource use per cycle	Values were sourced for one period only. Optometrist visit costs were assumed equal to ophthalmologist appointments.	Resource use per cycle was assumed to be constant for all cycles. This assumption was validated by a UK clinical expert.[105] In the absence of data in the literature, ophthalmologist appointments were

Factor	Assumed values	Justification
		considered suitably similar to an optometrist visit to constitute a proxy.
Market share	Within class and across class market shares are based on a UK sales data trend of December 2015 – December 2022. This analysis was conducted by Santen	It is assumed that sales data from December 2015 – December 2022 is reflective of the current market (in 2023). This selection of data was considered broad enough to reflect longer term trends, whilst still providing an up-to-date reflection of the current market.
Comparator unit dosing and treatment costs	It is assumed that a unit dose applies for one infected eye	When sourcing pack information from the BNF, it is assumed that a unit dose applies for one infected eye. When converting ml doses to drops, a 0.05 ml per drop conversion factor is applied, for all comparators (not netarsudil-latanoprost). This value is based on commonly used values in the published literature.[84,85] Accordingly, it is assumed that for all ml dosed (non-unit dosed) comparators, treatment will be applied by ml with no wastage. This assumption and method was validated by a UK clinical expert.[105] It is important to note that the company has data on file (see Question B16) supporting the use of a smaller drop size for netarsudil-latanoprost which would reduce the overall cost of treatment.[86] Hence, the assumption used here is conservative.
Administration costs	Administration costs are assumed to be negligible for all the FDC therapies	The assumption that administration costs are negligible for all the FDC therapies considered in the model is based on the fact that they are all self-administered eye drops.
Transition matrices and source of efficacy data	For the netarsudil-latanoprost and bimatoprost-timolol matrices, transition probabilities for both study eye and fellow eye are informed by MERCURY 3 IPD.[6] An NMA was conducted to produce estimated transition counts for dorzolamide-timolol, brimonidine-timolol, brinzolamide-brimonidine, latanoprost-timolol and travoprost-timolol. Efficacy data were unavailable for the two remaining FDC	MERCURY 3 is the most appropriate source for netarsudil-latanoprost and bimatoprost-timolol efficacy data as this reflects the population of interest for this appraisal. The NMA attempts to reduce bias caused by the lack of a head-to-head trial comparing netarsudil-latanoprost to the FDC comparators of interest. Comparators in the same drug classes have an equivalent mechanism of action and are therefore expected to be of similar efficacy. In line with the lack of differentiation between study eye and fellow eye in

Factor	Assumed values	Justification
	comparators in the model (brinzolamide-timolol and tafluprost-timolol). Therefore efficacy was assumed equal to comparators of the same drug class. The efficacy of brinzolamide-timolol (CAI+BB) and tafluprost-timolol (PGA+BB) were assumed equal to dorzolamide-timolol and bimatoprost-timolol, respectively. The same NMA outputs are applied for both the study eye and fellow eye i.e.., it is assumed that the relative treatment effect between the two eyes is equivalent across comparators. The results of the random effects model were applied in the base case.	the literature, and appreciation of varying baseline IOP levels with the percentage-based heath states, the same NMA outputs are applied for both the study eye and fellow eye.
Transition matrix extrapolation: Average method applied in the base case	The Average method, employed in the base case, applies an average of the baseline-cycle 3 transition probability values to all remaining cycles. This assumes that patient improvement/worsening in IOP post-cycle 3 follows the same trend observed in cycles 1 to 3.	The 'Average' method is considered reflective of clinical expectations, as confirmed by a UK clinical expert.
Study eye and fellow eye	The NMA was based only on data for study eye. When determining the transitions between health states for both study and fellow eye, the same NMA output is applied to the differing transitions. While adverse events reporting for most comparators included both study eye and fellow eye, some costing may only pertain to the study eye. All costs in the model, which are based on the treatment of two eyes, are applied with the assumption that	The literature for costs did not differentiate between study eye and fellow eye and were thus assumed to apply similarly to both. In line with the lack of differentiation between study eye and fellow eye in the literature, and appreciation of varying baseline IOP levels with the percentage-based heath states, the same NMA outputs are applied for both the study eye and fellow eye i.e.., it is assumed that the relative treatment effect between the two eyes is equivalent across comparators.

Factor	Assumed values	Justification
	study eye and fellow eye costs do not differ.	
Concomitant treatments	The uptake of SLT and/or trabeculectomy was assumed to be consistent across the intervention and all comparators. No other concomitant treatments were included in the model, asides a second line of treatment.	In the absence of treatment-specific data, it was assumed that the uptake of SLT and/or trabeculectomy was consistent across the intervention and all comparators. Uptake for SLT and/or trabeculectomy was based on NHS secondary care data, applying the 2022 rates to all years of the model for the '<20% reduction in IOP' health state. A 10% multiplier decrement was applied for the other health states to reflect reduced uptake from a decreasing IOP. It was also assumed, in line with MERCURY 3, that no other concomitant treatments would be taken by patients and impact costs, efficacy, or safety outcomes.
Second line of treatment	A second line of treatment is included in the model for patients who discontinue. All patients who discontinue move onto a generic fixed-dose comparator that is an average of all other comparators, weighted by the average predicted 5-year market share. It is assumed that patients only discontinue (change to the generic comparator) once. The omission of the original treatment in the average involves the expectation that patients are not re-treated with a regimen after discontinuing. All costs are applied using an equivalent structure to the first line.	The generic average comparator, weighted by market share, provides a fair reflection of the treatment setting, in which all model considered comparators are available to all patients. Patients not being retreated with the same regimen is informed by treatment guidelines. Accordingly, the literature did not indicate any significant difference between the treatment of fellow and study eyes. The 5-year market share average provides a broad but relevant indication of real-world expectations. Second line transitions were assumed to be equivalent to first line transitions, in line with the IPD from MERCURY 3 and prior treatment not being identified as a treatment effect modifier or prognostic variable both in the targeted literature search or by the clinical expert.
Persistence/discontinuation	The discontinuation (persistence) value for latanoprost-timolol, tafluprost-timolol, and	In the absence of individually sourced rates, it is assumed that comparators in the same class, that have an

Factor	Assumed values	Justification
	travoprost-timolol are assumed equal to bimatoprost-timolol. An extrapolated discontinuation (persistence) rate is applied for all comparators, based on the percentage change from month 1 to the remaining MERCURY 3 periods, for netarsudil-latanoprost and bimatoprost-timolol.	equivalent mechanism of action, have an equivalent discontinuation rate. The use of an extrapolated discontinuation rate is informed by clinicians.[87]In the absence of data, the netarsudil-latanoprost and bimatoprost-timolol discontinuation dynamic is assumed to be reflective of the comparators.
Wastage	Wastage is included in the base case. Wastage is captured as part of the cost per drop for all comparators and the intervention. The expiry once opened for each comparator/intervention is considered, comparing the pack size with the dosage within the expiry-life timeframe. Assuming that the remaining product is wasted at the end of the expiry-life, a proportion of waste product is calculated and the price per drop is increased by this proportion. In line with the assumption of 100% compliance, wastage is calculated assuming that there are no missed doses or lost or damaged product. The shelf life for each comparator is immaterial for the treatment horizon and assumptions. For unit doses, no wastage is included.	The unopened shelf life of the intervention is not considered material given the expected handling and provision of the medication; product is not expected to be distributed to patients for 2–3-year periods. Storage requirements for both opened and unopened medication were considered simple and therefore assumed to be fulfilled by all patients. Accordingly, no lost or damaged product is reasonably expected. Assuming wastage at the end of each cycle, follows the expectation that the decision to discontinue is made at each visit (cycle). In the event of discontinuation, it is expected that the remaining dosage would be entirely disposed of. Unit doses are packaged individually for each dose, so no wastage from expiry-life can be incurred. Compliance is assumed to be 100% based as the MERCURY 3 trial[6] and the model from NICE NG81[33] included no formal measure of compliance, noting that no commercially available method was available for direct, single-container monitoring of treatment adherence with multi-dose ophthalmic products. Compliance in the model is therefore assumed to be 100%, with persistence accounting for discontinuation within the trial. Scenario analyses are performed to test the impact of compliance on model results

Factor	Assumed values	Justification
Patient utility	HSUVs were estimated using MERCURY 3 trial data, by mapping SF-36 observations to EQ-5D utility indices, using a mapping algorithm published in Ara *et al.* (2008). Mean utilities were then estimated for each health state and applied directly in the model. Utilities for each AE were applied in the model for their average duration observed in the MERCURY 3 trial. If AEs did not occur in the trial (abnormal vision, conjunctival bleeding, eyelash discolouration) it was assumed conservatively, that the AEs were one cycle long. If an AE end date was not reported, a value of 120 days was applied, translating to application in all cycles (cycle 4+/treatment duration). AE durations were rounded to the nearest cycle length (i.e., nearest 30 days).	Ara and Brazier (2008)[70] was considered appropriate for mapping SF-36 data, as the algorithms were developed using a dataset collected in the UK and included patient observations with various indications. The Ara and Brazier (2008)[70] method was selected for the base case, due to its alignment with existing utility values in the literature. An equivalent regression method (Brazier and Roberts 2004) as Ara and Brazier (2008) had previously been utilised for mapping SF-36 data to EQ-5D as published in NICE HST5.[74,75] A scenario has been included using the mapping algorithm from Rowen *et al*. (2009)[73]. A scenario has also been included using QoL values from Stein et al. 2012[51] and Orme et al 2012[41]. These manage uncertainty and demonstrate the accuracy of the base case. In the absence of data, the assumption that an AE will last one cycle is conservative. If an AE end date was not supplied, it is expected that the AE was ongoing at the end of the study period and therefore application in all cycles is reasonable.
Caregiver costs and quality-of-life	Not included in the economic analysis.	As confirmed by a UK clinical expert.

Abbreviations: AE– Adverse event; BB – Beta-blocker; BNF– British National Formulary; CEM – Cost-effectiveness model; COAG – Chronic open-angle glaucoma; EQ-5D – EuroQol 5 Dimensions; IOP – Intraocular pressure; ITT– Intention-to-treat; NICE, National Institute for Health and Care Excellence; OAG– open-angle glaucoma; OHT– Ocular hypertension; PGA – Prostaglandin analogue; POAG – Primary open-angle glaucoma; SF-36 – Short Form 36; UK - United Kingdom

Base case results

Base case incremental CEA results

This section presents the updated base case results of the CEA comparing netarsudil-latanoprost to FDC comparators in a population of patients with POAG or OHT. Base case results are presented using the list price for netarsudil-latanoprost.

Aggregate results

Deterministic results showing incremental costs, life years gained (LYG) and QALYs for each FDC comparator versus netarsudil-latanoprost is presented in Table 89. An incremental analysis showing the total costs, LYG, QALYs, ICER versus baseline and ICER versus previously shown comparator for each FDC therapy is presented in Table 90.

In the updated deterministic base case analysis, netarsudil-latanoprost is dominated by all FDC comparators except for travoprost-timolol, latanoprost-timolol and tafluprost-timolol.

In the deterministic base case analysis, netarsudil-latanoprost was associated with lower average costs (£[redacted]) when compared to latanoprost-timolol (£[redacted]), tafluprost-timolol (£[redacted]) and travoprost-timolol (£[redacted]), indicating that netarsudil-latanoprost is cost-saving versus these FDC comparators over a lifetime. Incremental costs between netarsudil-latanoprost and the FDC comparators ranged from -£[redacted] to £[redacted] indicating relatively minimal differences in costs between interventions over a lifetime horizon of 33 years.

Compared to netarsudil-latanoprost, brinzolamide-brimonidine was associated with incremental costs of -£[redacted] and incremental QALYs of [redacted] ([redacted]), resulting in netarsudil-latanoprost being dominated. Clinical experts have indicated that brinzolamide-brimonidine is not commonly used in UK clinical practice in this population; it is typically used as a third- or fourth-line treatment for patients who have tolerability issues. This is discussed further in Section B.3.12 in Document B of the original submission.

The difference in incremental QALYs between an FDC comparator versus netarsudil-latanoprost ranged between [redacted] (versus travoprost-timolol) and [redacted] (versus brimonidine-timolol). The extremely small differences in incremental QALYs indicate negligible differences in treatment efficacy between all therapies over a 33-year time horizon, supporting the consideration of a cost-comparison approach rather than a full incremental CEA.

Table 89: Deterministic base case incremental analysis (incremental results of each comparator vs. netarsudil-latanoprost)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs. incremental QALYs	net monetary benefit (NMB)
Netarsudil-latanoprost	[redacted]	13.036	[redacted]	[redacted]	-	[redacted]	-	[redacted]
Brinzolamide and timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominated	[redacted]
Travoprost and Timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominating	[redacted]
Dorzolamide and timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominated	[redacted]
Latanoprost and timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominating	[redacted]
Tafluprost and timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	18,759	[redacted]
Bimatoprost and timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominated	[redacted]
Brimonidine and timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominated	[redacted]
Brinzolamide and brimonidine	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominated	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

Table 90: Deterministic base case results (incremental results vs. treatment with lowest total costs)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs. incremental QALYs	NMB
Bimatoprost and timolol	[redacted]	13.036	[redacted]	[redacted]	-	[redacted]	-	[redacted]
Brinzolamide and timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominated	[redacted]
Dorzolamide and timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominated	[redacted]
Brinzolamide and brimonidine	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	41,529	[redacted]
Brimonidine and timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	63,664	[redacted]
Netarsudil-latanoprost	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominated	[redacted]
Latanoprost and timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominated	[redacted]
Tafluprost and timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominated	[redacted]
Travoprost and Timolol	[redacted]	13.036	[redacted]	[redacted]	0.000	[redacted]	Dominated	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

Disaggregated results

A summary of the QALY gains by health state for netarsudil-latanoprost versus each FDC comparator is presented in Table 91 to Table 98. It can be observed that the largest QALY gains for netarsudil-latanoprost were in the >30% reduction in IOP health state ([redacted]), followed by the 20% - 30% reduction in IOP health state ([redacted]) and finally, the <20% reduction in IOP health state ([redacted]). The greatest incremental difference in QALYs was observed in the 20 - 30% reduction in IOP and >30% reduction in IOP health states, for the comparison of netarsudil-latanoprost with latanoprost-timolol ([redacted] and [redacted], respectively).

Table 91: Summary of QALY gains by health state - netarsudil-latanoprost vs. brinzolamide-timolol

Health state	QALY Netarsudil-latanoprost	QALY Brinzolamide-timolol	Increment	Absolute increment	% absolute increment
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure; QALY – Quality-adjusted life year

Table 92: Summary of QALY gains by health state - netarsudil-latanoprost vs. dorzolamide-timolol

Health state	QALY Netarsudil-latanoprost	QALY Dorzolamide-timolol	Increment	Absolute increment	% absolute increment
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure; QALY – Quality-adjusted life year

Table 93: Summary of QALY gains by health state - netarsudil-latanoprost vs. latanoprost-timolol

Health state	QALY Netarsudil-latanoprost	QALY Latanoprost-timolol	Increment	Absolute increment	% absolute increment
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure; QALY – Quality-adjusted life year

Table 94: Summary of QALY gains by health state - netarsudil-latanoprost vs. tafluprost-timolol

Health state	QALY Netarsudil-latanoprost	QALY Tafluprost-timolol	Increment	Absolute increment	% absolute increment

<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure; QALY – Quality-adjusted life year

Table 95: Summary of QALY gains by health state - netarsudil-latanoprost vs. bimatoprost-timolol

Health state	QALY Netarsudil-latanoprost	QALY Bimatoprost-timolol	Increment	Absolute increment	% absolute increment
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure; QALY – Quality-adjusted life year

Table 96: Summary of QALY gains by health state - netarsudil-latanoprost vs. travoprost-timolol

Health state	QALY Netarsudil-latanoprost	QALY Travoprost-timolol	Increment	Absolute increment	% absolute increment

<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure; QALY – Quality-adjusted life year

Table 97: Summary of QALY gains by health state - netarsudil-latanoprost vs. brimonidine-timolol

Health state	QALY Netarsudil-latanoprost	QALY Brimonidine-timolol	Increment	Absolute increment	% absolute increment
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure; QALY – Quality-adjusted life year

Table 98: Summary of QALY gains by health state - netarsudil-latanoprost vs. brinzolamide-brimonidine

Health state	QALY Netarsudil-latanoprost	QALY Brinzolamide-brimonidine	Increment	Absolute increment	% absolute increment

<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure; QALY – Quality-adjusted life year

A summary of the life years (LY) gains by health state for netarsudil-latanoprost versus each FDC comparator is presented in Table 99 to

Table ***106***. It can be observed that the largest LY gains for netarsudil-latanoprost were in the >30% reduction in IOP health state (10.165), followed by the 20% - 30% reduction in IOP health state (1.999) and finally, the <20% reduction in IOP health state (0.872).

Table 99: Summary of LY gains by health state - netarsudil-latanoprost vs. brinzolamide-timolol

Health state	LY Netarsudil-latanoprost	LY Brinzolamide-timolol	Increment	Absolute increment	% absolute increment
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure; LY – Life year

Table 100: Summary of LY gains by health state - netarsudil-latanoprost vs. dorzolamide-timolol

Health state	LY Netarsudil-latanoprost	LY Dorzolamide-timolol	Increment	Absolute increment	% absolute increment
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure; LY – Life year

Table 101: Summary of LY gains by health state - netarsudil-latanoprost vs. latanoprost-timolol

Health state	LY Netarsudil-latanoprost	LY Latanoprost-timolol	Increment	Absolute increment	% absolute increment
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure; LY – Life year

Table 102: Summary of LY gains by health state - netarsudil-latanoprost vs. tafluprost-timolol

Health state	LY Netarsudil-latanoprost	LY Tafluprost-timolol	Increment	Absolute increment	% absolute increment
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure; LY – Life year

Table 103: Summary of LY gains by health state - netarsudil-latanoprost vs. bimatoprost-timolol

Health state	LY Netarsudil-latanoprost	LY Bimatoprost-timolol	Increment	Absolute increment	% absolute increment
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure; LY – Life year

Table 104: Summary of LY gains by health state - netarsudil-latanoprost vs. travoprost-timolol

Health state	LY Netarsudil-latanoprost	LY Travoprost-timolol	Increment	Absolute increment	% absolute increment
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure; LY – Life year

Table 105: Summary of LY gains by health state - netarsudil-latanoprost vs. brimonidine-timolol

Health state	LY Netarsudil-latanoprost	LY Brimonidine-timolol	Increment	Absolute increment	% absolute increment
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure; LY – Life year

Table 106: Summary of LY gains by health state - netarsudil-latanoprost vs. brinzolamide-brimonidine

Health state	LY Netarsudil-latanoprost	LY Brinzolamide-brimonidine	Increment	Absolute increment	% absolute increment
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure; LY – Life year

A summary of the costs by health state for netarsudil-latanoprost versus each FDC comparator, using the list price, is presented in Table 107 to

Table ***114***. The largest proportion of costs for netarsudil-latanoprost were accrued in the >30% reduction in IOP health state (£[redacted]) followed by the 20% - 30% reduction in IOP health state (£[redacted]), and finally the <20% reduction in IOP health state (£[redacted]). The largest total incremental costs were observed between netarsudil-latanoprost and bimatoprost-timolol (£[redacted]), brinzolamide-timolol (£[redacted]) and dorzolamide-timolol (£[redacted]). Incremental costs were negative for the comparisons of netarsudil-latanoprost with latanoprost-timolol (-£[redacted]), tafluprost-timolol (-£[redacted]) and travoprost-timolol (-£[redacted]) indicating that netarsudil-latanoprost is cost-saving compared to these FDC comparators.

Table 107: Summary of costs by health state - netarsudil-latanoprost vs. brinzolamide-timolol

Health state	Cost (£) Netarsudil-latanoprost	Cost (£) Brinzolamide-timolol	Increment	Absolute increment	% absolute increment
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure

Table 108: Summary of costs by health state - netarsudil-latanoprost vs. dorzolamide-timolol

Health state	Cost (£) Netarsudil-latanoprost	Cost (£) Dorzolamide-timolol	Increment	Absolute increment	% absolute increment

<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure

Table 109: Summary of costs by health state - netarsudil-latanoprost vs. latanoprost-timolol

Health state	Cost (£) Netarsudil-latanoprost	Cost (£) Latanoprost-timolol	Increment	Absolute increment	% absolute increment
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure

Table 110: Summary of costs by health state - netarsudil-latanoprost vs. tafluprost-timolol

Health state	Cost (£) Netarsudil-latanoprost	Cost (£) Tafluprost-timolol	Increment	Absolute increment	% absolute increment

<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure

Table 111: Summary of costs by health state - netarsudil-latanoprost vs. bimatoprost-timolol

Health state	Cost (£) Netarsudil-latanoprost	Cost (£) Bimatoprost-timolol	Increment	Absolute increment	% absolute increment
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure

Table 112: Summary of costs by health state - netarsudil-latanoprost vs. travoprost-timolol

Health state	Cost (£) Netarsudil-latanoprost	Cost (£) Travoprost-timolol	Increment	Absolute increment	% absolute increment

<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure

Table 113: Summary of costs by health state - netarsudil-latanoprost vs. brimonidine-timolol

Health state	Cost (£) Netarsudil-latanoprost	Cost (£) Brimonidine-timolol	Increment	Absolute increment	% absolute increment
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure

Table 114: Summary of costs by health state - netarsudil-latanoprost vs. brinzolamide-brimonidine

Health state	Cost (£) Netarsudil-latanoprost	Cost (£) Brinzolamide-brimonidine	Increment	Absolute increment	% absolute increment
<20% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: IOP – Intraocular pressure

A summary of the predicted resource use by category of cost for netarsudil-latanoprost versus each FDC comparator, is presented in Table 115 to Table 122. For netarsudil-latanoprost, the largest proportion of costs were for the health state costs. The largest incremental difference in costs between treatments was due to the treatment costs, discontinued patient costs or adverse event costs.

Table 115: Summary of predicted resource use by cost category - netarsudil-latanoprost vs. brinzolamide-timolol

Item	Cost (£) Netarsudil-latanoprost	Cost (£) Brinzolamide-timolol	Increment	Absolute increment	% absolute increment
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Add-on treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued patient cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Table 116: Summary of predicted resource use by cost category - netarsudil-latanoprost vs. dorzolamide-timolol

Item	Cost (£) Netarsudil-latanoprost	Cost (£) Dorzolamide-timolol	Increment	Absolute increment	% absolute increment
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Add-on treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued patient cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Table 117: Summary of predicted resource use by cost category - netarsudil-latanoprost vs. latanoprost-timolol

Item	Cost (£) Netarsudil-latanoprost	Cost (£) Latanoprost-timolol	Increment	Absolute increment	% absolute increment
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Add-on treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued patient cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Table 118: Summary of predicted resource use by cost category - netarsudil-latanoprost vs. tafluprost-timolol

Item	Cost (£) Netarsudil-latanoprost	Cost (£) Tafluprost-timolol	Increment	Absolute increment	% absolute increment

Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Add-on treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued patient cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Table 119: Summary of predicted resource use by cost category - netarsudil-latanoprost vs. bimatoprost-timolol

Item	Cost (£) Netarsudil-latanoprost	Cost (£) Bimatoprost-timolol	Increment	Absolute increment	% absolute increment
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Add-on treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued patient cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Table 120: Summary of predicted resource use by cost category - netarsudil-latanoprost vs. travoprost-timolol

Item	Cost (£) Netarsudil-latanoprost	Cost (£) Travoprost-timolol	Increment	Absolute increment	% absolute increment
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Add-on treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued patient cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Table 121: Summary of predicted resource use by cost category - netarsudil-latanoprost vs. brimonidine-timolol

Item	Cost (£) Netarsudil-latanoprost	Cost (£) Brimonidine-timolol	Increment	Absolute increment	% absolute increment
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Add-on treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued patient cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Table 122: Summary of predicted resource use by cost category - netarsudil-latanoprost vs. brinzolamide-brimonidine

Item	Cost (£) Netarsudil-latanoprost	Cost (£) Brinzolamide-brimonidine	Increment	Absolute increment	% absolute increment
Treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Add-on treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued patient cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Sensitivity analysis

Probabilistic sensitivity analyses (PSA) and one-way sensitivity analysis (OWSA) have been performed and are presented below. Key areas of uncertainty tested in sensitivity analyses included health state costs, adverse event costs and utility values. Scenario analyses explore parameter and scenario uncertainty.

Probabilistic sensitivity analysis

A PSA was conducted to estimate the uncertainties in the key model parameters. The analysis involved varying the inputs by randomly assigning a parameter value from predefined uncertainty distributions.

This was performed for each parameter simultaneously over multiple iterations, and the resulting incremental cost and QALY predictions were recorded. To ensure stability in results, it was decided to run 10,000 iterations for the base case analysis.

Where the standard errors for the parameters were unknown, they were assumed to be 20% of the parameter value for the purposes of defining the PSA distributions. For event rates and utilities, a beta distribution was used to restrict draws between 0 and 1. For costs and resource use estimates, a gamma distribution was fitted to prevent values less than zero.

Mean incremental results were recorded and illustrated through an incremental cost-effectiveness plane (ICEP). In addition, a cost-effectiveness acceptability curve (CEAC) was plotted.

Table 123 shows the mean results of the PSA comparing the FDC with the lowest treatment cost versus all other comparators. Probabilistic costs, LYs and QALYs are generally consistent with the deterministic results. Netarsudil-latanoprost was associated with a total cost of £[redacted] and mean total QALYs of [redacted]. The mean probabilistic results are similar to the base case for all comparators.

The ICEP is presented in Figure 18, and shows that netarsudil-latanoprost is generally more costly but less effective than most FDC comparators, with mean PSA points displayed in the north-west quadrant. Netarsudil-latanoprost is less costly and less effective than tafluprost-timolol and more effective and less costly than latanoprost-timolol and travoprost-timolol.

Table 123: PSA incremental results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Bimatoprost and timolol	[redacted]	12.710	[redacted]	[redacted]	-	[redacted]	-
Brinzolamide and timolol	[redacted]	12.710	[redacted]	[redacted]	0.000	[redacted]	Dominated
Dorzolamide and timolol	[redacted]	12.710	[redacted]	[redacted]	0.000	[redacted]	Dominated
Brinzolamide and brimonidine	[redacted]	12.710	[redacted]	[redacted]	0.000	[redacted]	161,815
Brimonidine and timolol	[redacted]	12.710	[redacted]	[redacted]	0.000	[redacted]	10,902
Netarsudil-latanoprost	[redacted]	12.710	[redacted]	[redacted]	0.000	[redacted]	Dominated
Latanoprost and timolol	[redacted]	12.710	[redacted]	[redacted]	0.000	[redacted]	Dominated
Tafluprost and timolol	[redacted]	12.710	[redacted]	[redacted]	0.000	[redacted]	Dominated
Travoprost and Timolol	[redacted]	12.710	[redacted]	[redacted]	0.000	[redacted]	Dominated

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Figure 18: ICEP for netarsudil-latanoprost versus FDC comparators

Abbreviations: FDC – Fixed-dose combination; ICEP – Incremental cost-effectiveness plane; PSA – Probabilistic sensitivity analysis; QALYs – Quality-adjusted life years

The CEAC is displayed in Figure 19 to illustrate the probability of netarsudil-latanoprost being cost-effective compared to comparators at various willingness-to-pay thresholds.

Figure 19: CEAC for netarsudil-latanoprost versus FDC comparators

Abbreviations: CEAC – Cost-effectiveness acceptability curve; FDC – Fixed-dose combination

Deterministic sensitivity analysis

A OWSA was used to assess the effect of parameter variation on net monetary benefit (NMB). The OWSA was performed using a SE approach. Where the SE was not available for a parameter, the SE was assumed to be 20% of the mean value. Based on its mean and the SE, the parameter was then varied using a 95% confidence interval based on the distribution of the parameter.

A tornado diagram was developed to graphically present the parameters for all variables which have the greatest effect on the NMB, at a willingness-to-pay (WTP) threshold of £30,000 per QALY.

The OWSA was performed for netarsudil-latanoprost compared to each FDC comparator in the model. The results are presented in the subsections below.

Netarsudil-latanoprost versus brinzolamide-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB, for the comparison of netarsudil-latanoprost with brinzolamide-timolol is presented in Figure 20, with tabulated results presented in Table 124. The model was most sensitive to the second-line cost per cycle of netarsudil-latanoprost and brinzolamide-timolol.

Figure 20: OWSA tornado diagram for netarsudil-latanoprost versus brinzolamide-timolol: NMB

Abbreviations: IOP – Intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Table 124. Tabulated OWSA results for netarsudil-latanoprost versus brinzolamide-timolol: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)

2nd line netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	£1,566
2nd line brinzolamide-timolol cost per cycle (£)	-£1,247	£250	£1,496
Utility: >30% reduction in IOP	-£330	-£797	£468
Utility: 20% - 30% reduction in IOP	-£730	-£422	£308
Netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	£237
Brinzolamide-timolol cost per cycle (£)	-£642	-£485	£157
Utility: <20% reduction in IOP	-£625	-£519	£106
>30% reduction in IOP total cost	-£617	-£515	£102
Netarsudil-latanoprost adverse event total cost (cycle 4+)	-£536	-£613	£77
Proportion of patients treated with add-on trabeculectomy: >30% reduction in IOP	-£605	-£530	£75

Abbreviations: IOP – Intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Netarsudil-latanoprost versus dorzolamide-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB for the comparison of netarsudil-latanoprost with dorzolamide-timolol is presented in Figure 21, with tabulated results presented in Table 125. The model was most sensitive to the second-line cost per cycle of netarsudil-latanoprost and dorzolamide-timolol.

Figure 21: OWSA tornado diagram for netarsudil-latanoprost versus dorzolamide-timolol: NMB

Abbreviations: IOP – Intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Table 125. Tabulated OWSA results for netarsudil-latanoprost versus dorzolamide-timolol: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
2nd line netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	£1,566
2nd line dorzolamide-timolol cost per cycle (£)	-£1,108	£393	£1,500
Utility: >30% reduction in IOP	-£189	-£657	£468
Utility: 20% - 30% reduction in IOP	-£590	-£281	£308
Netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	£237
Dorzolamide-timolol cost per cycle (£)	-£522	-£318	£204
Utility: <20% reduction in IOP	-£484	-£378	£106
>30% reduction in IOP total cost	-£476	-£374	£102
Netarsudil-latanoprost adverse event total cost (cycle 4+)	-£395	-£472	£77
Proportion of patients treated with add-on trabeculectomy: >30% reduction in IOP	-£464	-£389	£75

Abbreviations: IOP – intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Netarsudil-latanoprost versus latanoprost-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB for the comparison of netarsudil-latanoprost with latanoprost-timolol is presented in

Figure 22, with tabulated results presented in Table 126. The model was most sensitive to the second-line cost per cycle of netarsudil-latanoprost and latanoprost-timolol.

Figure 22: OWSA tornado diagram for netarsudil-latanoprost versus latanoprost-timolol: NMB

Abbreviations: IOP – Intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Table 126. Tabulated OWSA results for netarsudil-latanoprost versus latanoprost-timolol: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
2nd line netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	£1,566
2nd line latanoprost-timolol cost per cycle (£)	-£43	£808	£851
Latanoprost-timolol cost per cycle (£)	-£26	£787	£813
Latanoprost-timolol adverse event total cost (cycle 4+)	£184	£533	£348
Latanoprost-timolol adverse event total disutility (cycle 4+)	£194	£521	£328
Utility: >30% reduction in IOP	£482	£210	£272
Netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	£237
Utility: 20% - 30% reduction in IOP	£239	£437	£198
Netarsudil-latanoprost adverse event total cost (cycle 4+)	£376	£299	£77
Netarsudil-latanoprost adverse event total cost (cycle 1)	£370	£307	£64

Abbreviations: IOP – Intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Netarsudil-latanoprost versus tafluprost-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB for the comparison of netarsudil-latanoprost with tafluprost-timolol is presented in Figure 23, with tabulated results presented in Table 127. The model was most sensitive to the second-line cost per cycle of netarsudil-latanoprost and the utility for the >30% reduction in IOP health state.

Figure 23: OWSA tornado diagram for netarsudil-latanoprost versus tafluprost-timolol: NMB

Abbreviations: IOP – Intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Table 127. Tabulated OWSA results for netarsudil-latanoprost versus tafluprost-timolol: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
2nd line netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	£1,566
Utility: >30% reduction in IOP	£431	-£637	£1,067
Tafluprost-timolol cost per cycle (£)	-£562	£417	£979
2nd line tafluprost-timolol cost per cycle (£)	-£491	£332	£823
Utility: <20% reduction in IOP	-£340	£95	£435
Tafluprost-timolol adverse event total cost (cycle 4+)	-£276	£71	£348
Utility: 20% - 30% reduction in IOP	-£251	£3	£255
Netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	£237
>30% reduction in IOP total cost	-£224	£8	£232
<20% reduction in IOP total cost	-£32	-£226	£195

Abbreviations: IOP – Intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Netarsudil-latanoprost versus bimatoprost-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB for the comparison of netarsudil-latanoprost with bimatoprost-timolol is presented in Figure 24, with tabulated results presented in

Table ***128***. The model was most sensitive to the second line cost of Netarsudil-latanoprost per cycle, the utility for the >30% reduction in IOP health state and the bimatoprost-timolol cost per cycle.

Figure 24: OWSA tornado diagram for netarsudil-latanoprost versus bimatoprost-timolol: NMB

Abbreviations: IOP – Intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Table 128: Tabulated OWSA results for netarsudil-latanoprost versus bimatoprost-timolol: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
2nd line netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	£1,566
Utility: >30% reduction in IOP	-£225	-£1,292	£1,067
Bimatoprost-timolol cost per cycle (£)	-£1,250	-£197	£1,053
2nd line bimatoprost-timolol cost per cycle (£)	-£984	-£521	£463
Utility: <20% reduction in IOP	-£995	-£560	£435
Utility: 20% - 30% reduction in IOP	-£906	-£652	£255
Netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	£237
>30% reduction in IOP total cost	-£880	-£647	£232
<20% reduction in IOP total cost	-£687	-£881	£195
Proportion of patients treated with add-on trabeculectomy: >30% reduction in IOP	-£852	-£681	£171

Abbreviations: IOP – Intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Netarsudil-latanoprost versus travoprost-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB for the comparison of netarsudil-latanoprost with travoprost-timolol is presented in Figure 25, with tabulated results presented in

Table ***129***. The model was most sensitive to the utility values for the >30% reduction in IOP and 20-30% reduction in IOP health states and the second line cost per cycle of netarsudil-latanoprost.

Figure 25: OWSA tornado diagram for netarsudil-latanoprost versus travoprost-timolol: NMB

Abbreviations: IOP – intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Table 129: Tabulated OWSA results for netarsudil-latanoprost versus travoprost-timolol: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
Utility: >30% reduction in IOP	-£1,109	£3,703	£4,811
Utility: 20% - 30% reduction in IOP	£3,315	-£440	£3,754
2nd line netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	£1,566
>30% reduction in IOP total cost	£1,844	£798	£1,046
Utility: <20% reduction in IOP	£1,796	£959	£837
2nd line travoprost-timolol cost per cycle (£)	£1,000	£1,823	£824
Travoprost-timolol cost per cycle (£)	£1,006	£1,816	£811
Proportion of patients treated with add-on trabeculectomy: >30% reduction in IOP	£1,720	£950	£771
20% - 30% reduction in IOP total cost	£1,052	£1,759	£707
Proportion of patients treated with add-on trabeculectomy: 20% - 30% reduction in IOP	£1,121	£1,675	£554

Abbreviations: IOP – intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Netarsudil-latanoprost versus brimonidine-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB for the comparison of netarsudil-latanoprost with brimonidine-timolol is presented in Figure 26, with tabulated results presented in

Table ***130***. The model was most sensitive to the utilities for the >30% reduction in IOP and 20-30% reduction in IOP health states and the second line cost per cycle of brimonidine-timolol and netarsudil-latanoprost.

Figure 26: OWSA tornado diagram for netarsudil-latanoprost versus brimonidine-timolol: NMB

Abbreviations: IOP – intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Table 130: Tabulated OWSA results for netarsudil-latanoprost versus brimonidine-timolol: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
Utility: >30% reduction in IOP	£503	-£1,744	£2,247
Utility: 20% - 30% reduction in IOP	-£1,649	£271	£1,920
2nd line brimonidine-timolol cost per cycle (£)	-£1,385	£229	£1,614
2nd line netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	£1,566
>30% reduction in IOP total cost	-£876	-£388	£488
20% - 30% reduction in IOP total cost	-£492	-£854	£361
Proportion of patients treated with add-on trabeculectomy: >30% reduction in IOP	-£818	-£459	£360
Utility: <20% reduction in IOP	-£817	-£498	£319
Proportion of patients treated with add-on trabeculectomy: 20% - 30% reduction in IOP	-£527	-£811	£283
Netarsudil-latanoprost cost per cycle (£)	-£548	-£786	£237

Abbreviations: IOP – intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Netarsudil-latanoprost versus brinzolamide-brimonidine

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB for the comparison of netarsudil-latanoprost with brinzolamide-brimonidine is presented in Figure 27, with tabulated results presented in

Table ***131***. The model was most sensitive to the second-line cost per cycle of netarsudil-latanoprost and brinzolamide-brimonidine.

Figure 27: OWSA tornado diagram for netarsudil-latanoprost versus brinzolamide-brimonidine: NMB

Abbreviations: IOP – intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Table 131: Tabulated OWSA results for netarsudil-latanoprost versus brinzolamide-brimonidine: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
2nd line netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	£1,566
2nd line brinzolamide-brimonidine cost per cycle (£)	-£1,236	£284	£1,520
Utility: >30% reduction in IOP	-£167	-£909	£742
Utility: 20% - 30% reduction in IOP	-£794	-£321	£472
Netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	£237
Brinzolamide-brimonidine cost per cycle (£)	-£649	-£429	£220
Utility: <20% reduction in IOP	-£638	-£463	£175
>30% reduction in IOP total cost	-£622	-£461	£161
Proportion of patients treated with add-on trabeculectomy: >30% reduction in IOP	-£603	-£484	£119
20% - 30% reduction in IOP total cost	-£509	-£598	£89

Abbreviations: IOP – intraocular pressure; NMB – Net monetary benefit; OWSA – One-way sensitivity analysis

Scenario analysis

Various scenario analyses were conducted to investigate the impact of using alternative assumptions. These include:

- Varying the BNF costs considered (drug tariff price and NHS indicative price)
- Varying the compliance rate (90% and 80% for all comparators)
- Varying the long-term efficacy extrapolation method (LOCF and final)
- Varying the persistence rate
  - Apply Sall *et al*. (2003) values for dorzolamide-timolol and brimonidine-timolol and Whitson *et al*. (2013) for brinzolamide-brimonidine
- Not applying age-adjusted utilities
- Varying the discount rate (1.5% costs and 3.5% outcomes, 3.5% costs and 1.5% outcomes, and 1.5% costs and 1.5% outcomes)
- Varying the time horizon (5 years and 15 years)
- Varying transition probabilities for brinzolamide-brimonidine (set equal to bimatoprost-timolol)
- Varying the transition probability method using fellow eye patient-level data (for netarsudil-latanoprost and bimatoprost-timolol)
- Varying the adverse event probabilities (base case rate doubled and tripled)
- Varying the QoL mapping method (Rowen *et al*. 2009)
- Varying the health state utility values (Stein *et al*. [2012] and Orme *et al*. [2012])
- Not applying wastage
- Varying the health state resource use multiplier
  - 3.5% and 5% (to reflect non-linearity of health state definitions)
  - 5% & 10% (double original values)
  - 10% and 15% (higher values + reflects non-linearity of health state definitions)
- Varying the NMA methodology (fixed effect)

Scenario analysis varying the BNF costs considered

A scenario analysis was conducted varying the BNF costs considered. The scenarios explored were drug tariff price and NHS indicative price (Table 132).

Table 132: Scenario analysis varying the BNF costs considered (incremental results vs. netarsudil-latanoprost)

BNF costs considered	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
Drug tariff price	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]
NHS indicative price	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]

Abbreviations: BNF – British National Formulary; ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NHS – National Health Service; QALYs – Quality-adjusted life years

Scenario analysis varying the compliance rate

A scenario analysis was conducted varying the compliance rate of all comparators, to explore the impact of applying a reduced compliance rate. The compliance rates explored were 90% and 80%, relative to a 100% compliance rate at baseline (Table 133).

Table 133: Scenario analysis varying the compliance rate (incremental results vs. netarsudil-latanoprost)

Compliance rate	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
90% for all comparators	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]
80% for all comparators	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Scenario analysis varying the extrapolation method for long-term efficacy estimates

A scenario analysis was conducted varying the extrapolation method used to generate long-term efficacy. The extrapolation methods explored were LOCF and assuming patients remain in their final health state (Table 134).

Table 134: Scenario analysis varying the extrapolation method for long-term efficacy estimates (incremental results vs. netarsudil-latanoprost)

Extrapolation method	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
LOCF	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]
Final	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LOCF – Last observation carried forward; LYG – Life years gained; QALYs – Quality-adjusted life years

Scenario analysis varying the persistence rate

Scenario analyses were conducted varying the persistence rate of each comparator. The persistence rate for all comparators, except bimatoprost-timolol, was set equal to the persistence rate of netarsudil-latanoprost and persistence data from Sall et al. (2003) values for dorzolamide-timolol and brimonidine-timolol and Whitson et al. (2013) for brinzolamide-brimonidine were applied (

Table ***135***).

Table 135: Scenario analysis varying the persistence rate (incremental results vs. netarsudil-latanoprost)

Persistence rate	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
Apply Sall *et al*. (2003) values for dorzolamide-timolol and brimonidine-timolol and Whitson *et al*. (2013) for brinzolamide-brimonidine	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Scenario analysis not applying age-adjusted utilities

A scenario analysis was conducted where age-adjusted utilities were not applied (Table 136).

Table 136: Scenario analysis not applying age-adjusted utilities (incremental results vs. netarsudil-latanoprost)

Age-adjusted utilities applied?	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
No	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Scenario analysis varying the discount rate

A scenario analysis was conducted varying the discount rate, to explore the impact of applying a reduced rate to future costs and outcomes. The discount rate combinations explored were: 1.5% costs and 3.5% outcomes, 3.5% costs and 1.5% outcomes and 1.5% costs and 1.5% outcomes, relative to a 3.5% discount rate at baseline for both costs and outcomes (Table 137).

Table 137: Scenario analysis varying the discount rate (incremental results vs. netarsudil-latanoprost)

Discount rate	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
1.5% costs and 3.5% outcomes	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]
3.5% costs and 1.5% outcomes	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]
1.5% costs and 1.5% outcomes	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]

	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Scenario analysis varying the time horizon

A scenario analysis was conducted changing the time horizon to 5 and 15 years (Table 138).

Table 138: Scenario analysis varying the time horizon (incremental results vs. netarsudil-latanoprost)

Time horizon	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
5 years	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]
15 years	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Scenario analysis varying the transition probabilities for brinzolamide-brimonidine

A scenario analysis was conducted to change the transition probabilities for brinzolamide-brimonidine to be equal to bimatoprost-timolol (Table 139).

Table 139: Scenario analysis varying the brinzolamide-brimonidine transition probabilities (incremental results vs. netarsudil-latanoprost)

Brinzolamide-brimonidine transition probabilities	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
Equal to bimatoprost-timolol	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Scenario analysis varying the transition probability method

Scenario analyses were conducted to change the transition probabilities for to the fellow eye for netarsudil-latanoprost and bimatoprost-timolol (Table 140).

Table 140: Scenario analysis varying the transition probability method (incremental results vs. netarsudil-latanoprost)

Transition probability method	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
Fellow eye transition probabilities	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Scenario analysis varying the AE probabilities

Scenario analyses were conducted varying the AE probabilities, to double and triple the base case rates (Table 141).

Table 141: Scenario analyses varying the AE probabilities (incremental results vs. netarsudil-latanoprost)

Multiplier applied to AE probabilities	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
Base case rate doubled	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]
Base case rate tripled	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]

Abbreviations: AE – adverse event; ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Scenario analysis varying the QoL mapping method

A scenario analysis was conducted to apply a different mapping method for the conversion of SF-36 data to EQ-5D. For this scenario, the method from Rowen *et al.* was applied (Table 142).[73]

Table 142: Scenario analysis varying the QoL mapping method (incremental results vs. netarsudil-latanoprost)

Methodology for mapping of QoL data	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
Rowen *et al.* 2009[73]	Netarsudil-latanoprost	-	-	-	-	-
	Brinzolamide-timolol	420.54	0.00	0.00	Dominated	Dominated
	Dorzolamide-timolol	328.68	0.00	0.00	Dominated	Dominated
	Latanoprost-timolol	-53.18	0.00	0.01	Dominating	Dominating
	Tafluprost-timolol	-199.33	0.00	-0.01	29,728.84	27,895.65
	Bimatoprost-timolol	612.72	0.00	0.00	Dominated	Dominated
	Brimonidine-timolol	261.89	0.00	0.00	Dominated	Dominated
	Travoprost-timolol	-202.17	0.00	0.02	Dominating	Dominating
	Brinzolamide-brimonidine	324.62	0.00	0.00	Dominated	Dominated

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years; QoL – Quality-of-life

Scenario analysis varying the health state utility values

Scenario analyses were conducted varying the health state utility values, using values sourced from the published literature that were identified from the targeted database searches (Table 141).

Table 143: Scenario analyses varying the health state utility values (incremental results vs. netarsudil-latanoprost)

Health state utility value source	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
Stein *et al*. (2012)[51]	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]
Orme *et al*. (2012)[41]	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Scenario analysis not applying wastage

Scenario analyses were conducted to not apply wastage (Table 140).

Table 144: Scenario analysis not applying wastage (incremental results vs. netarsudil-latanoprost)

Wastage	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
Not applying wastage	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Scenario analysis varying the health state resource use multipliers

Scenario analyses were conducted (Table 140) varying the health state resource use multipliers from 2.5% and 5%, respectively, to the following:

- 3.5% and 5% (to reflect non-linearity of health state definitions)
- 5% & 10% (double original values)
- 10% and 15% (higher values + reflects non-linearity of health state definitions)

Table 145: Scenario analysis varying the health state resource use multiplier (incremental results vs. netarsudil-latanoprost)

Health state resource use multiplier	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
3.5% and 5%	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]
5% and 10%	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]
10% and 15%	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]

	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Scenario analysis varying the NMA methodology

Scenario analyses were conducted varying the NMA methodology using the results from the fixed effect model (Table 140).

Table 146: Scenario analysis varying the NMA methodology (fixed effect model) (incremental results vs. netarsudil-latanoprost)

NMA methodology	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
Fixed effect model results	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMA – network meta-analysis; QALYs – Quality-adjusted life years

Scenario analysis varying the weighting of product costs within comparators

Scenario analyses were conducted varying the weighting of product costs within comparators, where comparator costs were based on the lowest-cost drug within each class (Table 147).

Table 147: Scenario analysis varying the weighting of product costs within comparators (comparator costs based on lowest-cost drug within each class)

Weighting of product costs	Technologies	Deterministic				Probabilistic
		Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)	ICER (£)
Comparator costs based on cheapest product within class	Netarsudil-latanoprost	[redacted]	-	[redacted]	[redacted]	[redacted]
	Brinzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Dorzolamide-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Latanoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Tafluprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Bimatoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brimonidine-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Travoprost-timolol	[redacted]	0.00	[redacted]	[redacted]	[redacted]
	Brinzolamide-brimonidine	[redacted]	0.00	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Summary of sensitivity analyses results

- In the probabilistic sensitivity analysis:
    - Probabilistic costs, LYs and QALYs were generally consistent with deterministic results. Netarsudil-latanoprost was associated with a total cost of [redacted] and mean total QALYs of [redacted]; mean probabilistic results are similar to the base case.
    - The ICEP shows that netarsudil-latanoprost is generally more costly than most FDC comparators and less effective however, the greatest incremental QALY difference between any treatment was only [redacted]. The ICEP also shows that netarsudil-latanoprost is less costly and less effective than tafluprost-timolol and more effective and less costly than latanoprost-timolol and travoprost-timolol.
    - The majority of the iterations in the PSA were plotted in the north-west quadrant of the ICEP, demonstrating that netarsudil-latanoprost is generally more costly but less effective than the FDC comparators. As previously described, however, the greatest incremental QALY difference between any treatment was only [redacted].
    - The CEAC demonstrates that bimatoprost-timolol has the highest probability of being the most cost-effective treatment at all WTP thresholds up to £25,000. At all WTP thresholds above £25,000, brimonidine-timolol has the highest probability of being the most cost-effective treatment.
- In the deterministic sensitivity analysis:
    - Across the comparators, NMB results were most sensitive to the second line treatment costs.
    - The largest difference in NMB observed for a single parameter is £4,811, indicating moderate stability in the model results.

- In the scenario analyses, incremental costs were generally stable across all scenarios. Care should be taken when considering ICER changes as the small magnitude of incremental QALYs between the comparators creates an extreme sensitivity to the ICERs. The scenario with the most notable impact was for bimatoprost-timolol in the scenario analyses applying a 1.5% discount rate to both costs and outcomes, as well as the scenario applying a 1.5% discount rate to costs and a 3.5% discount rate to outcomes (change in incremental costs from £[redacted] to £[redacted]).

Interpretation and conclusions of economic evidence

The results from the deterministic base case analysis show that, over a lifetime time horizon, netarsudil-latanoprost is associated with lower average costs (£[redacted]) when compared to latanoprost-timolol, tafluprost-timolol and travoprost-timolol demonstrating that netarsudil-latanoprost is cost-saving vs. these FDC comparators. Incremental costs between netarsudil-latanoprost and the FDC comparators ranged from -£[redacted] to £[redacted] indicating relatively minimal differences in costs between interventions over a lifetime horizon of 33 years. Over a lifetime time horizon, the maximum difference in QALYs between netarsudil-latanoprost and comparators is -0.039, indicating that the treatments considered have a similar effect on patient quality-of-life; this demonstrates that a cost-comparison approach is the most suitable incremental analysis method for this appraisal.

The mean results of the PSA were similar to the base case, confirming the deterministic results; netarsudil-latanoprost was associated with mean total costs of £[redacted] and mean total QALYs of [redacted]. The results from the PSA indicate that netarsudil-latanoprost is the second-cheapest treatment considered. Results for the OWSA and scenario analyses were also robust and demonstrated similar findings.

The availability of netarsudil-latanoprost as a new class of medication will allow treatment access to patients with intolerances or insufficient response to current IOP lowering medications. This will help lower the need for glaucoma surgery and reduce the risk of developing irreversible sight loss in patients with a previous unmet need, as well as decrease the direct and indirect costs associated.

Overall, this economic analysis shows that netarsudil-latanoprost may be considered a cost-saving and effective use of NHS resources for patients with POAG or OHT. It will provide an alternative treatment option in the management of these conditions, with a novel mechanism of action, for patients who are underserved by currently available therapies.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Netarsudil-latanoprost for previously treated primary open-angle glaucoma or ocular hypertension [ID1363]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Glaucoma UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Glaucoma UK is the UK's charity for people with glaucoma. We aim to prevent glaucoma sight loss, by raising awareness of the disease, helping people live well with their condition, supporting high-quality research into glaucoma, and influencing policy and practice regarding glaucoma care. We are funded entirely by our supporters, with the majority of our funding coming from legacies. We also receive some support from corporate sponsors such as pharmaceutical companies, but they have no influence on our messaging. We have around 4000 members, half of whom are people living with glaucoma, and the other half are glaucoma professionals.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Funding received from Santen for the following, in 2023: £20,000 for sponsorship of UKEGS (professional conference) for which they enjoyed branding and attendance at the event 22 and 23 November. £3500 for sponsorship of a challenge event completed by a professional Glaucoma UK member. £2149 to support reprint of a booklet providing patients with information about Dry Eye Disease (no editorial input), £9000 to co-develop and promote survey asking for information about patients' experiences of using eye drops sent to our members, supporters etc.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Engagement with members of our consultation panel (patient volunteers), discussion with relevant staff members such as helpline advisors.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	"Living with the condition is very difficult because you do not know from one consultation visit to the next whether the drugs are working and your pressure is being kept down and, even if this is the case, whether further visual damage has occurred." "Managing the numerous daily eye-drops can be very disruptive – as a child, I was unable to administer these myself and so relied heavily on my parents coming to school three or four times a day to support me, which was equally disruptive for them…. Another major factor is the uncertainty that comes with living with a chronic condition for which there is no cure, particularly when (as in my case) the condition has been volatile and will flare up very quickly without much warning. This means that I am always aware of my glaucoma, and on some level, always bracing myself for a further round of surgery, a bigger operation, more invasive treatments, etc." "My obvious fear is blindness. Frustration that they say it's genetic and not much can change that." Many patients describe the anxiety associated with glaucoma. Early stages are symptomless, so you don't know what's happening with your condition between appointments. This is exacerbated by the lack of agency people feel – no lifestyle factors you can change have been proven to improve your prognosis. The most common treatment (eye drops) can be more tiresome than the condition itself, causing itchy, sore eyes, and needing patients to manage repeat prescriptions, polypharmacy etc. Not all treatments are successful, for example the 2nd most common treatment (laser) usually only works for a few years and needs to be repeated. Its success diminishes over time, without the patient knowing, increasing anxiety. Another contributing factor is the fact you have to notify the DVLA if you have glaucoma in both eyes, causing additional uncertainty regarding loss of independence and mobility. Sight loss is irreversible, so people may feel they're on borrowed time, and that they have to do everything in their power to limit damage to vision, creating stressful expectations. Dealing with the NHS is stressful, in terms of delayed appointments, seeing lots of different clinicians and experiencing long waits in clinics. Most people with glaucoma are older, exacerbating challenges, for example in accessing appointments or instilling eye drops. Understanding of the disease can be limited, resulting in a reluctance to engage in condition and poorer adherence to treatment. Carers often have to help with the disease, for example instilling eye drops or taking to appointments. Depending on the patient, carers may also have to help with daily living, such as bathing or cooking. Given the uncertainty regarding prognosis, people don't know how long they may have good vision for, and have to put plans in place that may or may not need to be activated.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	"There is no cure for glaucoma. Once you have it, you are in for a rollercoaster of operations and lifelong use of drops." "Overall, my treatment on the NHS has been fantastic – I have had a lot of surgeries, but as a result I've retained good sight in one eye and am able to work, live alone and have a relatively 'normal' daily life. However, it is disruptive, and it can be difficult to manage." Patients are usually grateful when they receive treatment and care, but there are huge delays with appointments, especially post-COVID. The delivery of glaucoma care is changing, which some patients and carers find unsettling. People are more likely to be seen by allied healthcare professionals such as nurses or optometrists, in different settings, such as community hubs or optometric practices. If they don't understand why these changes are being made it, people may feel like they're being fobbed off, by not seeing a doctor in a hospital. There is a postcode lottery around care, with different doctors preferring to offer different treatments, or commissioning variability. This is unsettling for patients and carers. Appointments can be rushed, with limited opportunities to speak to a doctor (particularly in newer community settings etc), so people might leave without feeling like the care provider knows how that individual is coping, or without the care provider being able to check that the patient has understood the implications of the treatment/prognosis etc. Treatments address the symptoms of glaucoma, not the root cause, and don't restore lost vision, meaning some patients don't engage fully as they see it as a lost cause. The most common treatments are eye drops, laser and surgery. Eye drops are a challenge – they can be difficult to put in, and they make your eyes sore. The regime can involve using different drops multiple times a day, which can be burdensome and confusing. Stats around adherence are hard to find, but a significant proportion of patients don't adhere to their treatment. Laser is scary. Surgery even more so. Treatment is usually effective and people are grateful to receive it, but the lack of agency exacerbates existing anxiety around the condition.
8. Is there an unmet need for patients with this condition?	"There is a need, of course, for a cure or for a treatment which reverses sight loss." Earlier diagnosis and raising awareness of glaucoma as half the people with the disease don't know they have it. Better, more consistent support for people with glaucoma, so they understand their condition and receive help when and how they want it. This would also improve adherence to eye drops, so their glaucoma is better managed. Better understanding as to why some people respond well to certain treatments (such as laser or classes of eye drops) and others don't. People want to feel optimistic about their condition, and in control. Many patients ask for effective, regular monitoring, particularly that can be carried out at home (for example home eye pressure testing kits). They are also desperate for a cure to be found, which would restore lost vision.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	"It is clear that a drop which combined two of the drugs and only needs to be use once a day would be very advantageous. It makes it much more likely that the schedule will be followed correctly and this should result in better and more consistent outcomes good for the patient and value for money for the NHS." "As someone who has cycled through many different drops and types of drops throughout my treatment, one advantage would be to give medical staff another option to consider before further surgery." It is always good to have more options for treatment, and to provide alternatives for people who don't respond to the existing cohort of treatments. It provides people with new hope of protecting their vision, because the netarsudil works via a different mechanism to existing eye drops. It is exciting as a patient to see that research does sometimes come to fruition and that glaucoma isn't completely neglected! Netarsudil-latanaprost is a once-daily combination drop, which is easier to manage than multiple eye drops, multiple times a day. It also provides patient choice as it doesn't contain a beta-blocker, unlike most combination drops – many people can't use beta-blockers due to contraindications.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	"I cannot see any disadvantages as the side effects are the same ones as all glaucoma drops have." There are no disadvantages of this eye drop intrinsically, but all eye drops have downsides! (Described above.) It is disappointing that it still contains a preservative, as these are known to cause side effects such as sore eyes, inflammation of the conjunctiva and dry eye. The side effects of this drop may be worse than for other drops, such as red eye. Many drops are difficult to instil, as the bottle can be hard to squeeze, or the lid can be hard to remove. Has due consideration been given to its application in design or is it going to be another drop that people struggle to administer?

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	People who haven't responded to other therapies, or who want or need to take combination drops to minimise the number of different types of eye drops. People who cannot tolerate preservative in their eye drops will not benefit from this. Many people develop this intolerance over time, so patients who have used eye drops for some time may not benefit as much. Some patients have great difficulty putting in drops poor sight, shaky hands etc so the fewer drops they or their carers have to use the better.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No groups with protected characteristics have been identified. However, we would want due consideration to be given to usability of the bottle design, or support available to improve this, to ensure those with a disability can administer their drops. The usual issues of free prescription availability across the 4 nations of the UK apply – some people in the UK will be able to access this for free and others won't.

Other issues

13. Are there any other issues that you would like the committee to consider?	"If at all possible, I think it would be important to make the medication preservative free, as there are many patients who can't tolerate preservatives because of damage to the cornea caused by drops and surgery." It may be worth the committee looking at how it is used elsewhere worldwide, and the benefits/ drawbacks that they have found. Which patients should be offered this drop? Who will particularly benefit? And where should it be introduced in the treatment paradigm? There are many treatment options, but evidence on who would benefit and the best order to try treatments is scant. We recommend further research into this area.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Eye drops are a cornerstone of glaucoma treatment, but are difficult to manage correctly and patient adherence is a known issue. • We support the introduction of new therapies which increase patient choice and improve the likelihood that an effective treatment will be found for everyone with glaucoma. • Effective support for people using this treatment must be offered, for example guidance on how to manage eye drops or dispensing aids to improve instillation. • Living with glaucoma is scary, people are afraid of losing vision, and they want cause for optimism and hope. •

Thank you for your time.

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Netarsudil-latanoprost for previously treated open-angle glaucoma or ocular hypertension [ID1363]

Produced by Aberdeen HTA Group

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Moira Cruickshank reviewed and critiqued the clinical effectiveness evidence presented in the company submission; Neil Scott and Dolapo Ayansina checked and critiqued the statistical analyses presented in the company submission; Dwayne Boyers, Rodolfo Hernández, and Mohammad Azharuddin reviewed and critiqued the cost-effectiveness evidence and economic model presented in the company submission; Paul Manson checked and critiqued the company's search strategies; Augusto Azuara-Blanco and Gianni Virgili provided clinical guidance and comments on the draft report. Miriam Brazzelli coordinated all aspects of this appraisal. All authors contributed to the writing of this report and approved its final version.

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List of abbreviations

AE	Adverse event
AH	Aqueous humor
ALT	Argon laser trabeculoplasty
ANCOVA	Analysis of Covariance
BB	Beta blocker
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COAG	Chronic open-angle glaucoma
DDTAE	Discontinuation due to adverse events
DSU	Decision Support Unit
EGS	European Glaucoma Society
EMA	European Medicines Agency
ERG	Evidence Review Group
ESS	Effective sample size
ETDRS	Early Treatment Diabetic Retinopathy Study
EVP	Episcleral venous pressure
FDC	Fixed-dose combination
FSH	Follicle-stimulating hormone
HCRU	Healthcare resource use
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
HTA	Health Technology Assessment
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
IOP	Intraocular pressure
IPD	Individual patient-level data

ITC	Indirect treatment comparison
ITT	Intention-to-treat
LASIK	Laser-assisted in situ keratomileusis
LOCF	Last observation carried forward
LS	Least square
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MCMC	Markov Chain Monte Carlo
NEI	National Eye Institute
NHS	National Health Service
NHSCII	NHS cost inflation index
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
OAG	Open-angle glaucoma
OHT	Ocular hypertension
OHTS	Ocular Hypertension Treatment Study
OTC	Over the counter
OWSA	One-way sensitivity analysis
PGA	Prostaglandin analogue
PLD	Patient-level data
POAG	Primary open-angle glaucoma
PP	Per-protocol
PPK	Photorefractive keratectomy
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QD	Once daily
QoL	Quality of life
RCT	Randomised controlled trial
RhoA	Ras homolog family member A
ROCK	Rho-(associated) coiled-coil containing protein kinase

RNFL	Retinal nerve fibre layer
SAE	Serious adverse event
SC	Schlemm's canal
SD	Standard deviation
SE	Standard error
SF-36	Short Form-36
SLR	Systematic literature review
SLT	Selective laser trabeculoplasty
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SOC	System organ class
STC	Simulated treatment comparison
TEAE	Treatment-emergent adverse event
TM	Trabecular meshwork
UD	Unit dose
UK	United Kingdom
WTP	Willingness-to-pay

1. Executive summary

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision-making. It also includes the EAG's preferred assumptions and the resulting impact on cost-effectiveness results.

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on cost-effectiveness. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology evidence and information on non-key issues are in the main EAG report. All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

A summary of the key issues for decision making are outlined below.

Table 1 Summary of key issues

Issue No.	Summary of issue	Report sections
1	The reliability of the results of the review of clinical effectiveness is questionable because of the non-systematic inclusion of monotherapies in the network meta-analysis.	Section 3.4.2
2	The company's economic model structure is not appropriate for a lifetime horizon assessment of cost-effectiveness because it does not capture the costs and QALY benefits of preventing or slowing conversion from OHT to glaucoma, or glaucoma disease progression.	Section 4.2.2
3	The company's post-treatment discontinuation assumptions do not reflect UK clinical practice and lack face validity. It is assumed that patients who discontinue treatment have the same IOP as those who remain on treatment. There are therefore no QALY implications of treatment discontinuation in the model. This is unlikely to be accurate, particularly over a longer-term time horizon.	Section 4.2.5
4	The company's approach to applying health state utility values creates uncertainty and their scenario analyses are inappropriate for decision making. There are no QALY implications of treatment discontinuation.	Section 4.2.6
5	The company's approach to costing relevant comparators assumes an average market share of branded (costed using NHS indicative prices) and generic (costed using drug tariff prices) products within class, prescribed in primary care. The EAG prefers to use drug tariff prices from the BNF for primary care, or the eMIT price for secondary care prescribing.	Section 4.2.7
6	The company assumes a much more intensive use of secondary care resources to manage mild and moderate adverse events than would be expected in UK clinical	Section 4.2.7

	practice.	

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are as follows:

- The company's preferred approach was to include only selected monotherapies in the network meta-analysis. The EAG prefers either to include all monotherapies from a systematic review or to pursue a more robust systematic approach to ensure effect estimates are not sensitive to the included trials or comparators. For example, they could have focused on a subset of monotherapy trials based on pre-specified criteria.

- The company prefers an economic model structure that captures intermediate, short-term changes in IOP, whereas the EAG is of the opinion that a model structure that uses a linked evidence approach to map changes in IOP to risk of conversion from OHT to glaucoma and risk of glaucoma disease progression. The EAG's preferred model structure would more appropriately capture the long-term implications of changes in IOP on costs and quality of life.

- The company preferred approach assumes comparator costs, based on average market shares of branded (costed using NHS indicative prices) and generic (costed using drug tariff prices) alternatives. The EAG accepts the company's market share data but prefers to use drug tariff prices as opposed to a combination of list prices and tariff prices. The EAG are of the view that the drug tariff price more accurately captures the price paid to pharmacies for dispensing the treatments in primary care.

- The company prefers to include more intensive management costs for adverse events, including multiple secondary care contacts for all patients experiencing events regardless of severity. The EAG's preferred adverse event costs are based on the EAG's clinical expert opinion and apply lower adverse event management costs.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained. In some scenarios, where QALYs are equal or similar, it may be appropriate to consider the cost implications of treatments.

Overall, there are minimal differences in QALYs between treatment arms in the model. This is partly driven by the EAGs concerns about the economic model structure. The minor QALY differences across treatments are due to:

- Slightly lower reductions in IOP, and thus slightly lower QALYs over time for netarsudil-latanoprost compared to bimatoprost-timolol and several other comparators.

- Higher adverse events for netarsudil latanoprost contributing to greater disutilities and lower QALYs compared to comparators.

Overall, the technology is modelled to affect costs by:

- Treatment acquisition costs for the first line of treatment are lower for netarsudil-latanoprost versus comparators due to higher modelled treatment discontinuation rates than, for example, bimatoprost-timolol.

- Higher comparator costs, driven using branded alternatives in the company's base case model.

- Higher costs of managing more frequently occurring adverse events for netarsudil-latanoprost vs. comparators.

The modelling assumptions that have the greatest effect on the ICER are:

- The economic model structural assumptions which do not model long-term costs and benefits of the full treatment or disease pathway for OHT and glaucoma.

1.3 The decision problem: summary of the EAG's key issues

The main change that the company made to NICE's final scope was to restrict treatment comparators to fixed-dose combination (FDC) therapies and to exclude both monotherapies and types of glaucoma surgery. The EAG's clinical advisers broadly agree with this decision as this reflects what would be available at the same stage on the treatment pathway as netarsudil-latanoprost.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The company's used different methodologies for the clinical effectiveness analyses in the original and revised submissions. The original submission used unanchored population-adjusted methods: simulated treatment comparisons (STC) and matching-adjusted indirect comparisons (MAIC). However, there are important limitations of these approaches, particularly that analyses could not be adjusted for all clinically relevant prognostic variables and effect modifiers, which means that they could be subject to bias of unknown magnitude. Furthermore, there were concerns about the searching process used for this submission which was only able to identify published articles between 2017 and 2022.

A revised submission was later received as part of the clarification process using a network meta-analysis (NMA) approach. As the treatment network was not connected, the company also used selected monotherapies in this analysis, but these were not chosen in a systematic way, and this could potentially introduce bias. The EAG accepts that to include all relevant monotherapies in the time available for the submission would be a major undertaking as there are significantly more published monotherapies than FDC trials, but it would have preferred a systematic approach to be used to ensure confidence in the results obtained (see Issue 1 below). The company's NMA approach leads to substantial uncertainty regarding the comparative treatment effects to be used in the economic model.

Issue 1 Reliability of the NMA findings

Report section	Section 3.4.2
Description of issue and why the EAG has identified it as important	The company included selected monotherapies in their NMA in order to achieve a connected network of therapies. This non-systematic inclusion of trials has the potential to result in biased treatment effect estimates.
What alternative approach has the EAG suggested?	More robust approaches should be considered, such as including all monotherapies or including monotherapy trials based on prespecified criteria, preferably agreed with clinical experts.
What is the expected effect on the cost-effectiveness estimates?	The use of a more robust approach would result in more reliable NMA estimates to be used in the economic modelling.
What additional evidence or analyses might help to resolve this key issue?	Evidence from a full systematic review including one or more types of monotherapy to achieve a connected network.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 2 The company's economic model structure

Report section	Section 4.2.2
Description of issue and why the EAG has identified it as important	The company's economic model structure does not adequately capture all relevant long-term costs and QALY benefits of changes in IOP. The model structure only considers short-term changes in IOP but does not link these to long-term costs and QALYs associated with disease progression. The EAG considers this to be an important issue because the quality of life and cost implications of preventing or reducing the risk of glaucoma progression are not captured in the economic model. This issue may materially impact on estimated total costs and total QALYs in the model. The impact on the ICER is unclear.
What alternative approach has the EAG suggested?	The EAG suggest that, for a full lifetime assessment of cost-effectiveness, the company should use a linked evidence approach to model the impact of changes in IOP on the risks of conversion from OHT to glaucoma and on the risk of glaucoma progression over time. The model structure suggested by the EAG is supported by clinical expert opinions (EAG clinical advisors) and consistent with several other glaucoma cost-effectiveness models.
What is the expected effect on the cost-effectiveness estimates?	The expected implications of adopting the EAG's preferred model structure are unknown.
What additional evidence or analyses might help to resolve this key issue?	A revised economic model would help reduce the uncertainty around this issue. Several published sources are available that the company could use to build an appropriate model structure. These are summarised in Table 10 of the EAG report.

Issue 3 The impact of treatment discontinuation on QALYs

Report section	Section 4.2.5
Description of issue and why the EAG has identified it as important	The company's economic model structure does not include any changes in transition probabilities or QALYs gained post treatment discontinuation. However, it does assume lower treatment acquisition costs for early discontinuation because patients discontinue to generic combination treatments over time. This is an important issue because the QALY benefits of effective treatments are likely to be underestimated in the model. It also leads to results that lead to questionable face validity, whereby it is more cost-effective to discontinue netarsudil-latanoprost than to remain on treatment.
What alternative approach has the EAG suggested?	A revised model structure that describes health states defined according to OHT and glaucoma disease progression could more appropriately link treatment discontinuation to the risk of disease progression.
What is the expected effect on the cost-effectiveness estimates?	The expected implications of adopting the EAG's preferred model structure are unknown.
What additional evidence or analyses might help to resolve this key issue?	A revised economic model would help reduce the uncertainty around this issue.

Issue 4 Health state utility values used in the model

Report section	Section 4.2.6
Description of issue and why the EAG has identified it as important	The health state utility values in the economic model do not capture the impact of glaucoma disease progression. There are also no QALY losses after treatment discontinuation for lack of effectiveness, despite the company's data suggesting people who discontinue have lower quality of life.
What alternative approach has the EAG suggested?	The EAG would consider a model that captures glaucoma disease progression to generate more appropriate QALYs. QALY decrements could also be modelled for multiple lines of treatment that follow glaucoma treatment pathways, up to and including surgery.
What is the expected effect on the cost-effectiveness estimates?	The implication is that long-term QALY estimates are likely to be over-estimated and the incremental QALY gains associated with the most effective IOP lowering treatments may be underestimated.
What additional evidence or analyses might help to resolve this key issue?	A revised model structure of glaucoma progression, with appropriate health state utility values obtained from the literature.

Issue 5 The costs of fixed dose combination therapy comparators used in the model.

Report section	Section 4.2.7
Description of issue and why the EAG has identified it as important	The company's preferred approach to costing relevant comparators uses product-specific market shares to guide the balance between branded and generic products within class, prescribed in primary care. The company's preferred approach applies NHS indicative pricing to branded and drug tariff pricing to generic alternatives. This issue is important because the EAG understand that this may over-estimate the costs to the NHS of primary care prescribing. This likely leads to a bias in cost-effectiveness results in favour of netarsudil-latanoprost.
What alternative approach has the EAG suggested?	The EAG prefers to use drug tariff prices in the base case analysis, obtained from the BNF, if prescribing typically takes place in primary care.
What is the expected effect on the cost-effectiveness estimates?	The EAGs approach would lead to higher incremental costs for netarsudil-latanoprost compared to other FDC comparators in the model.
What additional evidence or analyses might help to resolve this key issue?	The EAG would welcome further confirmation that all fixed-dose combination treatments for OHT, and glaucoma are typically prescribed and dispensed in primary rather than secondary care.

Issue 6 The resource use and costs of adverse events used in the economic model.

Report section	Section 4.2.7
Description of issue and why the EAG has identified it as important	The EAG's clinical expert opinion is that the resource use and costs of managing adverse events are overestimated compared to management in routine UK clinical practice. This is particularly relevant given that there were no Grade 3 or above adverse events observed in the MERCURY 3 trial. This issue is important because it means that costs for adverse events may be overestimated in the model. The company's approach may lead to a bias in cost-effectiveness results against treatments with higher adverse events, including netarsudil-latanoprost.
What alternative approach has the EAG suggested?	The EAG has sought clinical expert advice on alternative resource use assumptions.
What is the expected effect on the cost-effectiveness estimates?	The EAG's preferred approach would reduce the incremental costs for netarsudil-latanoprost versus comparators.
What additional evidence or analyses might help to resolve this key issue?	Further engagement with a range of UK clinical experts would be helpful to validate or refute the EAG's preferred resource use and ensure that adverse event management costs are generalisable across the UK.

1.6 Summary of EAG's preferred assumptions and resulting ICER

The EAG does not consider the company's economic model structure to meet the requirements of the NICE reference case, in that it does not capture all the relevant long-term costs and health consequences of changes in IOP. The EAG's preferred approach would be to build an economic model structure that captures all relevant long-term costs and QALYs. This could be achieved by using a linked evidence approach to model the impact of changes in IOP on the risk of conversion from OHT to glaucoma and the risk of glaucoma disease progression. The company could have drawn on examples from the published literature where this is achieved.

There has not been sufficient time within the STA process for the EAG to re-build the company's economic model using a preferred model structure. The EAG, therefore, believes that it would be misleading to present scenario analyses, applied to a model that is considered inappropriate for decision making. Committee may wish to consider short-term cost implications, for example over one year, where the impact of the model structure would have less of an impact on cost-effectiveness results. The EAG has provided several scenario analyses (Table 2) that present a simplified costing and cost-effectiveness assessment over a one-year time horizon. It should be noted that these analyses require strong assumptions of treatment efficacy equivalence, which have not been adequately demonstrated by the company's NMA. Assessments of equivalence compared to bimatoprost-timolol may be more appropriate, and the EAGs clinical experts are confident that the MERCURY 3 trial results rule out any clinically meaningful differences in IOP change between trial arms.

Table 2 Summary of the EAG's preferred assumptions applied to a one-year time horizon model (netarsudil latanoprost versus bimatoprost timolol).

	Scenario [B]	Total costs	QALYs	Incremental costs [A]	Incremental QALYs [A]	ICER [A]
1	**Company's base case (lifetime horizon, company preferred model structure)**					
	Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
2	**One year time horizon to minimize impact of model structural issues on results**					
	Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
3	**Apply equivalent ml/drop conversion factors to all treatments**					
	Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
4	**Apply drug tariff prices (assumes primary care prescribing)**					
	Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
5	**Apply EAG preferred adverse event resource use**					
	Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
6	**EAG's preferred assumptions, costs over a one year (Scenarios 2-5 combined)**					
	Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
7	**6 + Assume equal effectiveness**					
	Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	N/A

8	**6 + 7 + one full year on treatment (no treatment discontinuation)**					
	Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	N/A

Abbreviations: EAG: external assessment group; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

[A] Incremental analyses reported for netarsudil latanoprost vs. bimatoprost timolol. [B] Scenario analyses applied as univariate changes.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The relevant health conditions for the submission received from Santen Pharmaceuticals are previously treated open-angle glaucoma and ocular hypertension. The company's description of this health condition in terms of prevalence, symptoms and complications appears generally accurate and in line with the decision problem. The relevant intervention for this submission is netarsudil-latanoprost (Roclanda®).

2.2 Background

The company submission (CS) describes primary open-angle glaucoma (POAG) as a slow-developing, chronic, irreversible eye condition, exemplified by optic nerve damage, progressive loss of peripheral vision and then blindness. One of the major risk factors (and the only modifiable one) is increase of intraocular pressure (IOP), which is the pressure in the eye and is a delicate balance between the production and drainage of aqueous humor (AH).[1] Intraocular pressure is considered to be within normal limits between 11 and 21 mmHg with diurnal variance including higher pressures in the morning for some patients. More than 70 million people worldwide are estimated to be affected by glaucoma[2] with POAG being the most common form in the UK, affecting approximately 2% of people aged at least 40 years.[3] Hospital Episode Statistics for England for outpatients in the year 2021-2022 report 20,038 attendances for primary open-angle glaucoma (code H401).[4] In the early stages, POAG is often asymptomatic and early diagnosis is, therefore, challenging. Quality of life is affected by glaucoma in advanced stages, with more symptoms associated with poorer quality of life.[5-8] The goal of treatment of POAG is to slow disease progression and preserve quality of life by reducing IOP.[3, 9-14]

Elevated IOP, or IOP greater than 21 mmHg, in an otherwise healthy eye is also known as ocular hypertension (OHT). Ocular hypertension does not inevitably affect the vision but there is a strong association between OHT and development of glaucoma. Risk factors for developing glaucoma in people with OHT include age, family history, high IOP, thin cornea and high myopia.[15] Treatment of OHT aims to delay or prevent the progression of OHT to POAG by reducing the IOP.[16]

Current UK guidelines for treating people with POAG or OHT were published by NICE in 2017 and updated in 2022 (NG81).[17] These guidelines refer throughout to 'chronic open angle glaucoma' (COAG), which is interchangeable with POAG. Visual representations of the current treatment pathways for POAG and OHT are reported in Document B, Figure 4 and Figure 5, respectively, of the CS.

Summary of treatment recommendations for people with POAG:

Recommended initial treatment for people with newly diagnosed POAG is 360° selective laser trabeculoplasty (SLT). A second 360° SLT may be required if the effects of the initial procedure decrease over time. A generic prostaglandin (PGA) should be offered to people who are waiting for a 360° SLT and need an interim treatment or people who have already received 360° SLT but need their IOP reduced further. A generic PGA can also be offered to people who prefer not to have a 360° SLT or for whom a 360° SLT is not suitable.

For ongoing treatment, people who have adhered to treatment whose IOP has not been sufficiently reduced can be offered a medicine from another class, 360° SLT or glaucoma surgery with mitomycin C (MMC). For people who cannot tolerate a pharmacological treatment, a medicine from another therapeutic class or preservative-free eye drops (if the person is allergic to the preservative or has clinically significant and symptomatic ocular surface disease) can be offered.

For advanced POAG, surgery with MMC should be considered as an initial treatment and a generic PGA can be offered to those waiting for surgery. For people who choose not to have surgery or for whom surgery is not suitable, pharmacological treatment with combination of drops and 360° SLT or (occasionally) cyclodiode surgery can be offered. These treatments can also be offered to people who have had surgery but where IOP has not been sufficiently reduced. Further surgery can also be offered.

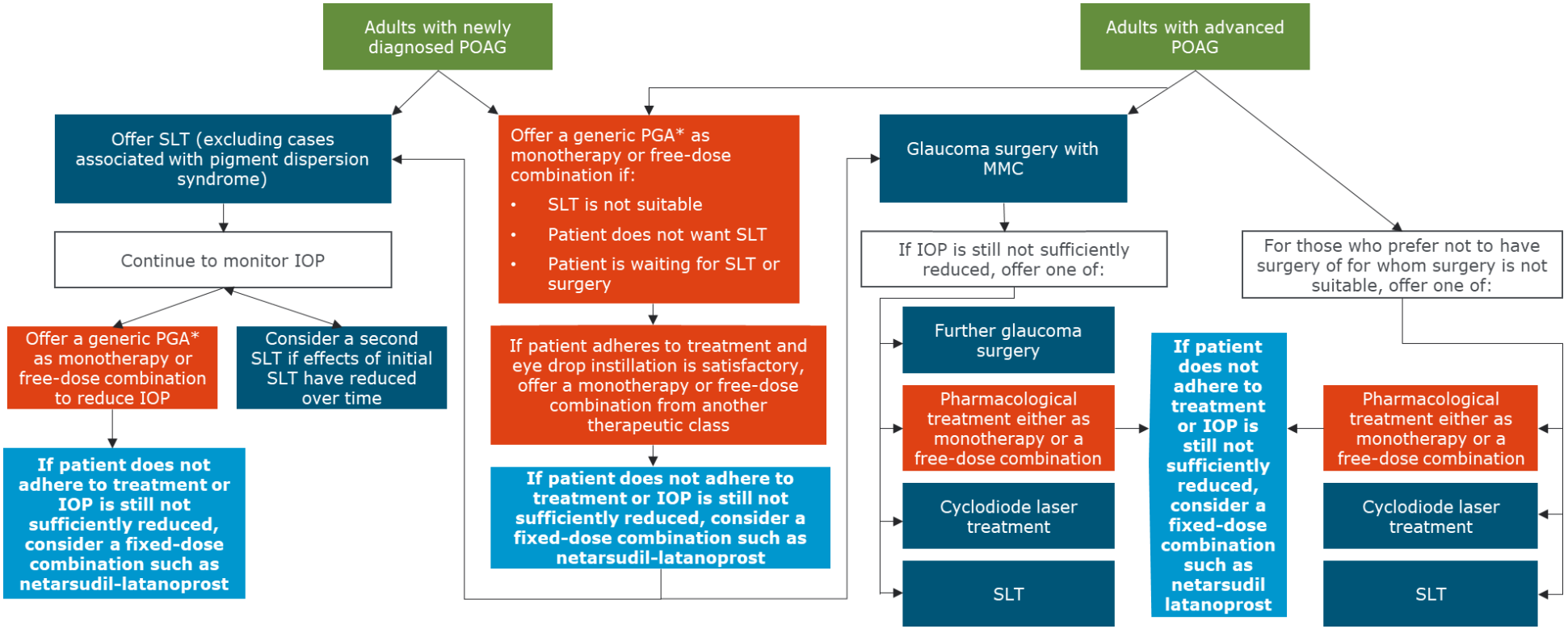
Summary of treatment recommendations for people with newly diagnosed OHT with IOP of ≥24 mmHg at risk of visual impairment within their lifetime:

For initial treatment, a 360° SLT should be offered, with a second procedure to be considered if the initial effect wears off. A generic PGA can be offered to people who are waiting for a 360° SLT and need an interim treatment or those for whom a 360° SLT has not sufficiently

reduced IOP. People who choose not to have a 360° SLT or for whom the procedure is not suitable can also be offered a generic PGA.

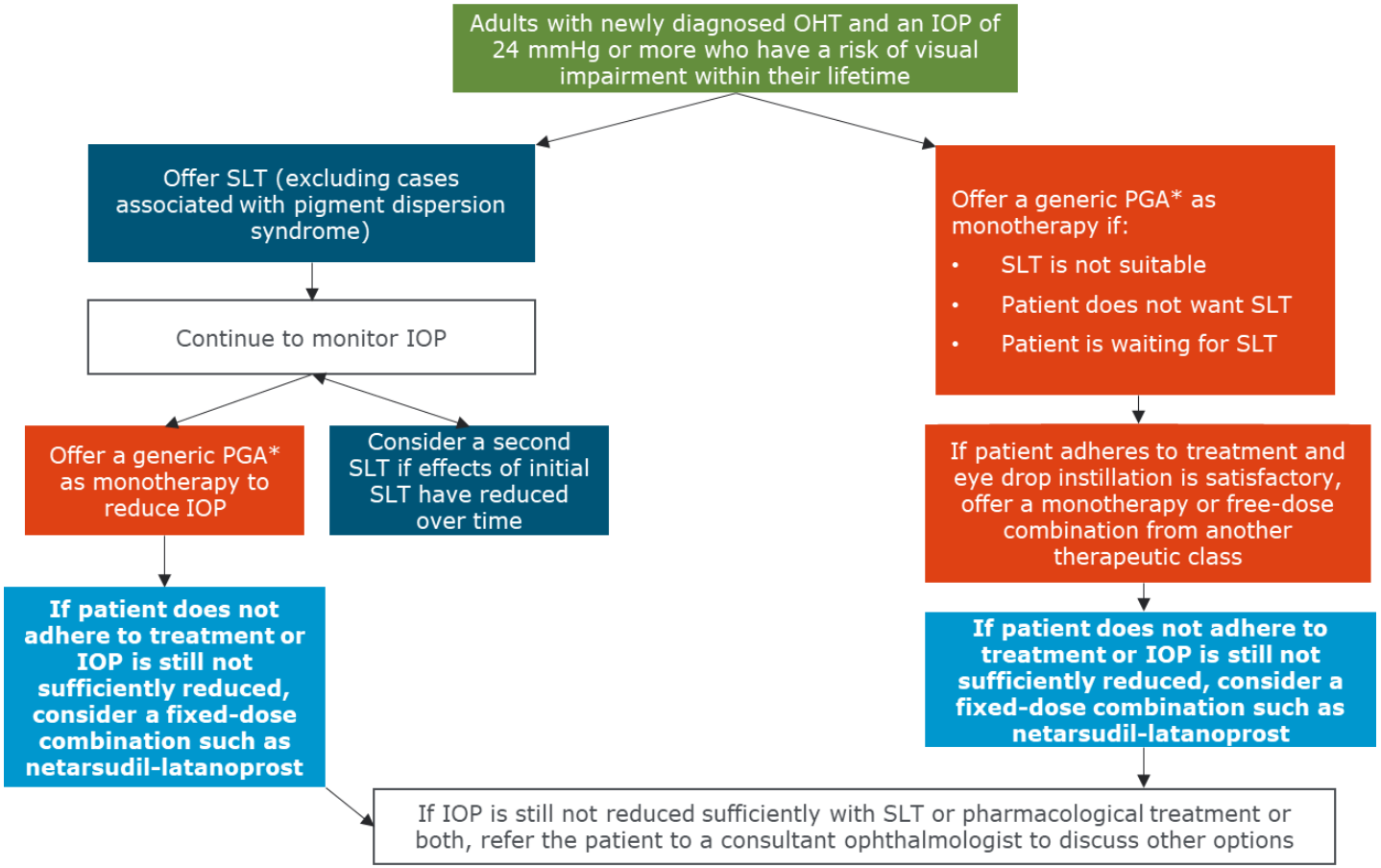
For ongoing treatment, another pharmacological treatment can be offered to people who cannot tolerate their current treatment and a medicine from another therapeutic class can be offered if current treatment is not sufficiently reducing IOP. People whose IOP cannot be sufficiently reduced with 360° SLT or pharmacological treatment, should be referred to a consultant ophthalmologist to discuss other treatment options.

Anticipated positioning of netarsudil-latanoprost in patients with POAG and OHT are presented in Document B, Figures 6 and 7, respectively, of the CS and reproduced as Figure 1 and Figure 2 below. The EAG clinical experts agree with the company's positioning of netarsudil-latanoprost in the care pathway.



*For patients who cannot tolerate a pharmacological treatment, a monotherapy or free-dose combination treatment from a different class can be considered such as a BB, CAI, or sympathomimetic. Alternatively, preservative-free eye drops can be used if there is evidence that the person is allergic to the preservative or has clinically significant and symptomatic ocular surface disease. Abbreviations: BB – Beta blocker; CAI – Carbonic anhydrase inhibitor; IOP – Intraocular pressure; MMC – Mitomycin C; PGA – Prostaglandin analogue; POAG – Primary open-angle glaucoma; SLT – Selective laser trabeculoplasty

Figure 1 Anticipated positioning of netarsudil-latanoprost in patients with POAG [reproduced from Figure 6, Document B of the company's submission]



*If a patient cannot tolerate their current treatment, offer an alternative generic PGA. If that is not tolerated, offer a BB. If neither of these options are tolerated, offer a non-generic PGA, a CAI, a sympathomimetic, a miotic, or a combination of treatments. Alternatively, preservative-free eye drops can be used if there is evidence that the person is allergic to the preservative or has clinically significant and symptomatic ocular surface disease. Abbreviations: BB – Beta blocker; CAI – Carbonic anhydrase inhibitor; IOP – Intraocular pressure; OHT – Ocular hypertension; PGA – Prostaglandin analogue; SLT – Selective laser trabeculoplasty

Figure 2 Anticipated positioning of netarsudil-latanoprost in patients with OHT [reproduced from Figure 7, Document B of company's submission]

2.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 3 below. A critique of how the company's economic modelling adheres to the NICE reference case is provided in Chapter 3.

Table 3 Summary of the company's decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with primary open-angle glaucoma or ocular hypertension whose intraocular pressure (IOP) has not improved after treatment with a prostaglandin or netarsudil	Adult patients with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction	Wording used to align with the marketing authorisation	The EAG agrees with the company's rationale
Intervention	Netarsudil-latanoprost (Roclanda®)	Netarsudil-latanoprost (Roclanda®)	In line with the NICE final scope	The intervention described in the CS matches that described in the NICE final scope. Netarsudil-latanoprost received a positive CHMP opinion in November 2020 and was granted regulatory approval by the European Commission via the European Commission Decision Regulatory Reliance Procedure on 8th January 2021.
Comparator(s)	• Topical (eye drops), monotherapy or in combination: o Prostaglandin analogues (for example bimatoprost, latanoprost, tafluprost, travoprost) o Beta-blockers (for	• FDC topical eye drops: o Prostaglandin analogues (for example bimatoprost, latanoprost, tafluprost, travoprost) o Beta-blockers (for	Netarsudil-latanoprost is licensed in adult patients for whom monotherapy with a prostaglandin or netarsudil has failed due to insufficient IOP reduction. Therefore, it is not appropriate to consider topical monotherapies as comparators, since netarsudil-latanoprost will	The EAG agrees that monotherapy treatments are not relevant at this point in the treatment pathway. However, the company used selected monotherapy trials to form a connected network for a network meta-analysis (NMA) as this could not be achieved for FDC therapies alone. The EAG

	example betaxolol, carteolol hydrochloride, levobunolol hydrochloride, timolol maleate) o Carbonic anhydrase inhibitors (for example acetazolamide, brinzolamide, dorzolamide) o Sympathomimetics (for example apraclonidine, brimonidine tartrate). • Selective laser trabeculoplasty • Other glaucoma surgery	example betaxolol, carteolol hydrochloride, levobunolol hydrochloride, timolol maleate) o Carbonic anhydrase inhibitors (for example acetazolamide, brinzolamide, dorzolamide) o Sympathomimetics (for example apraclonidine, brimonidine tartrate). In the revised analysis submitted at clarification, monotherapies were included but only as a bridge between different parts of a disconnected network in the network meta-analysis.	be offered once patients have failed on these. Furthermore, clinical expert opinion has advised that in UK clinical practice, netarsudil-latanoprost will be positioned in adult patients for whom free combination therapy has failed due to insufficient adherence. Netarsudil-latanoprost will therefore be positioned alongside other fixed-dose combination topical therapies, as aligned with UK clinical expert opinion. Selective laser trabeculoplasty and other glaucoma surgery are also not appropriate to consider as comparators as these will be offered to patients on top of or after treatment with netarsudil-latanoprost or other fixed-dose combination topical therapies.	supports this approach in principle but believes that either all monotherapies should have been included or a more systematic approach should have been used to ensure confidence in the results obtained. The EAG's clinical experts note that SLT should be first-line treatment (as described in Figure 6, Document B of the CS)

Outcomes	The outcome measures to be considered include: • Mean IOP • Visual acuity • Visual field test • Evaluation of anterior and posterior segment parameters • Structural integrity of the optic nerve • Adverse effects of treatment • HRQoL	In line with the primary and secondary endpoints in MERCURY 3, the following outcomes are captured in the economic model and the submission: • IOP • AEs • HRQoL	In line with the NICE final scope.	The EAG is satisfied with the company's approach. The EAG's clinical experts note that IOP is the most important efficacy outcome. Visual acuity is a safety outcome and not relevant in this context as only decreases in very serious disease or with serious adverse events. Visual field tests and structural tests are core outcomes for glaucoma studies but, realistically, will not change in trials of duration less that one to two years
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an	A cost-utility analysis was conducted in Microsoft Excel with the cost-effectiveness expressed in terms of an incremental cost per quality-adjusted life year. A lifetime time horizon was used (33 years). The analysis considers the benefit of treatment in the best and worst seeing eye. Costs were considered from an National Health Service and Personal Social Services perspective. Costs of biosimilar and generic products were taken	In line with the NICE final scope.	The EAG agrees that a cost-utility analysis using quality adjusted life years with a lifetime time horizon has been conducted. However, the company's economic model structure is not appropriate for a lifetime horizon assessment of cost-effectiveness because it does not capture the costs and QALY benefits of preventing or slowing conversion from OHT to glaucoma, or glaucoma disease progression. The EAG agrees that costs were

	NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account. Cost-effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.	into account.		considered from a National Health Service and Personal Social Services perspective. Commercial arrangements have been incorporated in the EAG model. The EAG is satisfied that the costs of generic products have been considered in so far as they have been included in the company's market share analysis. However, the EAG prefers the use of drug tariff pricing over list prices. The EAG is satisfied that best and worst seeing eyes have been incorporated into the economic model.

Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • Adult patients with primary open-angle glaucoma for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction. • Adult patients with ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction.	The evidence did not allow for subgroups to be considered.	In line with the NICE final scope.	The company conducted subgroup analyses of MERCURY 3 based on age, country (UK), prior hypotensive medication experience, and maximum baseline IOP value
Special considerations including issues related to equity or equality	Adults with primary open-angle glaucoma or ocular hypertension whose IOP has not improved after treatment with a prostaglandin or netarsudil	Adult patients with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction	Wording used to align with the marketing authorisation	The EAG is satisfied with the company's rationale

Abbreviations: AE – adverse event; HRQoL – health-related quality of life; IOP – Intraocular pressure; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; UK – United Kingdom

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company's evidence consisted of their original submission (June 2023) and their response to clarification questions (October 2023) for which revised analyses were undertaken. These two submissions contained important differences in the methods of searching, quality assessment and evidence synthesis. In the tables below, these are referred to as the "original" and "updated" reviews.

An important limitation of the original review was that only studies from 2017 to 2022 were included. At the clarification stage the EAG communicated that additional relevant RCTs from before 2017 were likely to be available and should be included. The company then conducted what they referred to as a "targeted" review. The EAG believes that the revised search is robust and should have identified all fixed dose combination (FDC) trials published before 2017.

NICE's final scope specified any topical FDC or monotherapy to be relevant comparators, as well as selective laser trabeculoplasty or other glaucoma surgery. The company's original submission examined only FDC comparators, but because of the need to create a connected network for a network meta-analysis (NMA) the revised targeted submission also included some RCTs with monotherapy comparators. Although these studies were identified from a systematic search, the inclusion of these studies appears to have been made in an arbitrary rather than a systematic way. The EAG's initial searches suggest around 100 RCTs comparing one of two types of monotherapy (netarsudil and latanoprost) could be available. This means that a full systematic review including both monotherapies and FDCs would be a major undertaking.

The EAG's appraisal of the company's systematic review methods is summarised in Table 4, which has been adapted to include both the original systematic review conducted by the company and the updated review reported at clarification. The search strategies in the updated review were reported but details of the methods used

to identify the studies were not, although it is assumed that the methods used were identical to the original review. Quality assessment of the identified studies was also not reported.

Table 4 EAG's appraisal of the systematic review methods presented in the company's submission

Review process EAG	ORIGINAL REVIEW: EAG response	UPDATED REVIEW: EAG response
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	The searches were limited to 2017-22, with no explanation given. The text terms searched were not comprehensive, and the searches were not equivalent between databases.	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details provided in Appendix D of the CS.
Were appropriate bibliographic databases/sources searched?	The HTA database searched via the CRD interface has not been updated since 2015 and no equivalent, current database of HTAs was included. Other sources were appropriate.	Sources included EMBASE, MEDLINE, and CENTRAL for primary research. Relevant conference proceedings and trial registers were also searched. Bibliographies of recent SLRs were examined to identify relevant studies not captured by the literature searches Full details are provided in Appendix D of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Searches were not restricted by any eligibility criteria. However, they were limited to fixed-dose comparators and monotherapies were excluded.	Searches were not restricted by any eligibility criteria. However, they were limited to fixed-dose comparators and monotherapies were excluded.
Was study selection conducted by two or more reviewers	Yes. Two independent reviewers were involved	Not reported

Review process EAG	ORIGINAL REVIEW: EAG response	UPDATED REVIEW: EAG response
independently?	in title/abstract screening and full-text screening.	
Was data extraction conducted by two or more reviewers independently?	No. Appendix D, Section D.2.1 states: "*Data were extracted by one reviewer and checked for accuracy by a second reviewer. Discrepancies were resolved through discussion or by consulting a third reviewer if necessary.*" The EAG is satisfied with this approach	Not reported
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes. The company used the guidelines of the NICE STA user guide	Not reported
Was the risk of bias assessment conducted by two or more reviewers independently?	No. At clarification, the company stated: "*One reviewer independently carried out the risk of bias assessment, which was then quality checked by a second reviewer. Any discrepancies were discussed, and a third reviewer involved if necessary to reach a decision.*" The EAG considers this strategy to be appropriate	4/9 studies in the NMA were assessed in the original submission. Assessment of the remaining five studies was not reported
Was identified evidence synthesised using appropriate methods?	Major concerns	Some concerns

The EAG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria. The results are presented in Table 5, adapted to include both the original and updated reviews. The main issue identified by the EAG relates to the completeness of the search strategies that do not involve a systematic search for all potentially relevant monotherapy comparators. In addition, quality assessment of the

five additional studies included in the updated review was not reported by the company.

Table 5 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	ORIGINAL REVIEW: Yes/No/Unclear	UPDATED REVIEW: Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes	Yes
2. Is there evidence of a substantial effort to search for all the relevant research?	No	No
3. Is the validity of included studies adequately assessed?	Yes	No
4. Are sufficient details of the individual studies presented?	Yes	Yes
5. Are the primary studies summarised appropriately?	Yes	Yes

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

Details of the key clinical effectiveness evidence are presented in Document B, Section B.2 of the CS. In the original submission the main clinical effectiveness for the clinical effectiveness and safety of netarsudil-latanoprost consisted of MERCURY 3: a phase III, multicentre, randomised, double-blind, active-controlled trial. The EAG has no major concerns about the design and conduct of this trial. An overview of MERCURY 3 is presented in Table 3, Document B of the CS and reproduced as Table 6 below. This is the only randomised study comparing netarsudil-latanoprost against another FDC (bimatoprost-timolol), although there are two other three-arm trials (MERCURY 1 and 2), which compare netarsudil-latanoprost against netarsudil and latanoprost as monotherapies.

Table 6 Clinical effectiveness evidence for netarsudil-latanoprost

[reproduced from Table 3, Document B of the company's submission]

Study	MERCURY 3 (NCT03284853)
Trial design	Prospective, double-blind, randomised (1:1), multicentre, active-controlled, parallel-group safety and efficacy trial, with a treatment and follow-up period of 180 days (six months)
Population	Adults (aged 18 years or older) with a diagnosis of open-angle glaucoma (OAG) or OHT in both eyes (a diagnosis of OAG in one eye and OHT in the fellow eye was acceptable), medicated IOP ≥17 mmHg in at least one eye and <28 mmHg in both eyes at the screening visit. • Number of patients *planned* recruited receiving: – Netarsudil-latanoprost (n=220) – Bimatoprost-timolol (n=220) • Number of patients *analysed* receiving: – Netarsudil-latanoprost (n=218) – Bimatoprost-timolol (n=212)
Intervention(s)	Latanoprost 0.005% ophthalmic solution and netarsudil mesylate 0.02%, taken as one drop in the affected eye(s) once daily in the evening; Alternative names: netarsudil-latanoprost, Roclanda, PG324
Comparator(s)	Bimatoprost 0.03% and timolol maleate 0.5% ophthalmic solution, taken as one drop in the affected eye(s) once daily, administered either in the morning or in the evening; Alternative names: bimatoprost-timolol, Ganfort
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale for use/non-use in the model	This study investigated netarsudil-latanoprost in the population to be treated as per the licensed indication, included a relevant comparator and includes key outcomes used in the economic model
Reported outcomes specified in the decision problem	*Primary endpoint:* • **Mean IOP within a treatment group at the following time points: 08:00, 10:00, and 16:00 hours at the week 2, week 6, and month 3 study visits** *Secondary endpoints:* • **Mean diurnal IOP within a treatment group at each post-treatment visit** • Mean change from diurnally adjusted baseline IOP at each post-treatment time point • Mean change from baseline in diurnal IOP at each post-treatment visit • Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point

	• Mean percent change from baseline in diurnal IOP at each post-treatment visit • Percentages of subjects achieving pre-specified mean, mean change, and percent mean change in diurnal IOP levels *Safety endpoints:* • **Adverse events (AEs)** • Heart rate and blood pressure • Biomicroscopy of anterior segment including evaluation of cornea, conjunctiva and anterior chamber • Dilated ophthalmoscopy • Best Corrected ETDRS Visual Acuity • Visual fields • Pachymetry • IOP • Clinical chemistry and haematology laboratory findings • Pregnancy testing (for women of childbearing potential) • Change in Self-Administered NEI Visual Functioning Questionnaire-25 (VFQ) score from baseline to study exit • **Change in Self-Administered Short Form Health Survey Questionnaire 36 (SF-36 V.2) score from baseline to study exit**
All other reported outcomes	N/A

Abbreviations: AE – Adverse event; ETDRS – Early Treatment Diabetic Retinopathy Study; IOP – Intraocular pressure; logMAR – logarithm of the minimum angle resolvable; mmHg – Millimetres of mercury; NEI – National Eye Institute; OAG – Open- angle glaucoma; OHT – Ocular hypertension; SF-36 – Self-Administered Short Form Health Survey Questionnaire 36; VFQ – Visual Functioning Questionnaire

The methods used by the MERCURY 3 study are reported in Document B, Section B.2.3 of the CS and key eligibility criteria are reported in Document B, Table 5. The primary objective of MERCURY 3 was to assess the ocular hypotensive effect of netarsudil-latanoprost relative to bimatoprost-timolol at 0800, 1000 and 1600 hours of the Week 2, Week 6, and Month 3 visits. Participant flow in MERCURY 3 is presented in Appendix D.3, Figure 5.3 of the CS. The trial was funded by Aerie Pharmaceuticals and conducted in 68 centres across 11 countries. A total of 35 participants were recruited from the 12 UK centres. A total of 430 participants were randomised.

Details of the baseline demographic and disease characteristics of MERCURY 3 are reported in Document B, Table 7 of the CS. In general, the baseline demographic characteristics were similar between the groups apart from sex; there were more

females (60.1%) than males (39.9%) in the netarsudil-latanoprost group but there were more males (56.6%) than females (43.4%) in the comparator group. Baseline disease characteristics were similar between groups; the sole exception being prior prostaglandin therapy (78.4% in the netarsudil-latanoprost group vs 69.3% in the bimatoprost-timolol group). The EAG's clinical experts agree with the company's assertion that this imbalance is unlikely to bias the results. More participants were diagnosed with OAG (56.9% in the netarsudil-latanoprost group; 52.8% in the bimatoprost-timolol group) than OHT (43.1%, 47.2%, respectively) in the study eye.

Overall, the EAG's clinical experts are satisfied that the baseline demographic and disease characteristics are representative of patients with OAG or OHT who would be eligible for this treatment in the UK.

3.2.2 Primary and secondary efficacy endpoints of MERCURY 3

The outcomes of MERCURY 3 reported in the CS are intraocular pressure (IOP), health-related quality of life (HRQoL) and adverse events. The primary population for efficacy analyses was the intention-to-treat (ITT) population, defined as all randomised participants who received at least one dose of study medication. The primary endpoint was mean IOP measured at three time points at each of three study visits (0800, 1000 and 1600 at Week 2, Week 6, and Month 3). This differs from the CS which used mean percentage change in IOP from baseline as the main outcome definition.

Mean IOP within a treatment group at the following time points: 08:00, 10:00, and 16:00 hours at the week 2, week 6, and month 3 study visits

Primary endpoint: Mean IOP at 0800, 1000 and 1600 hours at Week 2, Week 6 and Month 3

The company planned an interim analysis of the primary endpoint when all participants had completed three months of treatment, at which point, the trial was unblinded. Clinical non-inferiority was defined as the upper limit of the 95% confidence intervals (CIs) around the difference between the groups being ≤1.5 mmHg at all time points and ≤1.0 mmHg at most time points up until Month 3. The company presents details of the mean IOP (using Markov Chain Monte Carlo

(MCMC) imputation) at the nine specified time points in Document B, Table 9 of the CS (reproduced as Table 7 below).

Table 7 MERCURY 3 baseline-adjusted ANCOVAs for study eye IOP (mmHg) at each post-dose time point - ITT population with MCMC [reproduced from Document B, Table 9 of the CS]

	Netarsudil-latanoprost QD (N=218)	Bimatoprost-timolol QD (N=212)	Difference from bimatoprost-timolol
Week 2 (day 15), 08:00 hours			
n	218	212	-
LS mean (p-value)	[redacted]	[redacted]	0.17 (0.5581)
SE [95% 2-sided CI]	[redacted]	[redacted]	0.29 [0.40, 0.74]
Week 2 (day 15), 10:00 hours			
n	218	212	-
LS mean (p-value)	[redacted]	[redacted]	-0.17 (0.5193)
SE [95% 2-sided CI]	[redacted]	[redacted]	0.27 [-0.70, 0.35]
Week 2 (day 15), 16:00 hours			
n	218	212	-
LS mean (p-value)	[redacted]	[redacted]	-0.48 (0.0904)
SE [95% 2-sided CI]	[redacted]	[redacted]	0.28 [-1.03, 0.08]
Week 6 (day 43), 08:00 hours			
n	218	212	-
LS mean (p-value)	[redacted]	[redacted]	0.88 (0.0023)**
SE [95% 2-sided CI]	[redacted]	[redacted]	0.29 [-0.32, 1.44]
Week 6 (day 43), 10:00 hours			
n	218	212	-
LS mean (p-value)	[redacted]	[redacted]	0.40 (0.1510)
SE [95% 2-sided CI]	[redacted]	[redacted]	0.28 [-0.15, 0.94]
Week 6 (day 43), 16:00 hours			
n	218	212	-
LS mean (p-value)	[redacted]	[redacted]	-0.08 (0.7613)
SE [95% 2-sided CI]	[redacted]	[redacted]	0.28 [-0.63, 0.46]
Month 3 (day 90), 08:00 hours			

	Netarsudil-latanoprost QD (N=218)	Bimatoprost-timolol QD (N=212)	Difference from bimatoprost-timolol
n	218	212	-
LS mean (p-value)	[redacted]	[redacted]	0.66 (0.0163)*
SE [95% 2-sided CI]	[redacted]	[redacted]	0.28 [0.12, 1.20]
Month 3 (day 90), 10:00 hours			
n	218	212	-
LS mean (p-value)	[redacted]	[redacted]	0.42 (0.1706)
SE [95% 2-sided CI]	[redacted]	[redacted]	0.31 [-0.18, 1.03]
Month 3 (day 90), 16:00 hours			
n	218	212	-
LS mean (p-value)	[redacted]	[redacted]	0.19 (0.5126)
SE [95% 2-sided CI]	[redacted]	[redacted]	0.29 [-0.38, 0.76]

Source: MERCURY 3 CSR;[18] Abbreviations: CI – Confidence interval; IOP – Intraocular pressure; ITT – Intention-to-treat; MCMC – Markov Chain Monte Carlo; mmHg – Millimetres of mercury; QD – Once Daily; LS – Least square; SE – Standard error; *p-value <0.05; **p-value <0.01; ***p-value <0.001. The ANCOVA model has treatment as a factor and baseline as a covariate. Difference from bimatoprost-timolol, SE of the difference, 2-sided CIs, and p-values are based on an ANCOVA comparing netarsudil-latanoprost QD with bimatoprost-timolol QD.

The company stated that clinical non-inferiority of netarsudil-latanoprost was demonstrated versus bimatoprost-timolol in the ITT population. The least square mean IOP ranged from [redacted] mmHg to [redacted] mmHg in the netarsudil-latanoprost group and from [redacted] mmHg to [redacted] mmHg in the bimatoprost-timolol group across all visits.

The company carried out sensitivity analyses of the primary outcome using other imputation methods, namely, observed values, last observation carried forward (LOCF) and baseline observation carried forward (BOCF). The company report that analyses using observed values were in line with the primary analyses but clinical non-inferiority of netarsudil-latanoprost was not demonstrated for the analyses using LOCF or BOCF.

Secondary IOP endpoints

- **Mean diurnal IOP within a treatment group at each post-treatment visit (ITT population; MCMC imputation):** Document B, Table 11 of the CS reports the

baseline adjusted ANCOVAs for mean diurnal IOP. Mean diurnal IOP values were calculated as the mean of the three measurements at each visit. Clinical non-inferiority of netarsudil-latanoprost compared with bimatoprost-timolol was demonstrated, with mean IOPs ranging from 15.39 mmHg to 15.64 mmHg for the intervention group and from 15.19 mmHg to 15.56 mmHg for the comparator group and an upper limit of ≤1 mmHg of the 95%CI around the difference between the groups at the three visits.

- **Actual mean and mean change from diurnally adjusted baseline IOP at each post-treatment time point (ITT population):** Mean IOP ranged from [redacted] mmHg (Week 2, 1600hrs) to [redacted] mmHg (Week 6, 0800 hrs) for the netarsudil group and from [redacted] mmHg (Month 3, 1600hrs) to [redacted] mmHg (Week 2, 0800hrs) for the bimatoprost-timolol group. Mean change from baseline in IOP ranged from -9.94 mmHg (Week 2, 0800hrs) to -9.03 mmHg (Month 3, 1600hrs) in the netarsudil-latanoprost group and from -10.41 mmHg (Month 3, 0800hrs) to -8.45 mmHg (Week 2, 1600hrs) in the bimatoprost-latanoprost group. Differences in actual IOP between the two groups was statistically significant in 2/9 of the timepoints.
- **Mean change from baseline in diurnal IOP at each post-treatment visit (ITT population; MCMC imputation):** Change in mean diurnal IOP was similar in the two group at each post-treatment visit timepoint. At Month 3, change from baseline was [redacted] mmHg in the netarsudil-latanoprost group and [redacted] mmHg in the bimatoprost-timolol group.
- **Mean percent change from diurnally adjusted baseline IOP at each post-treatment timepoint (ITT population):** Mean percent change from baseline in diurnal IOP was similar for the netarsudil-latanoprost and bimatoprost-timolol groups at Week 2 ([redacted] and [redacted], respectively), Week 6 ([redacted] and [redacted], respectively) and Month 3 ([redacted] and [redacted], respectively) but numerically greater for the bimatoprost-timolol group at the Week 6 and Month 3 visits.
- **Mean percent change from baseline in diurnal IOP at each post-treatment visit (ITT population):** Mean percent change from baseline in diurnal IOP was similar between the netarsudil-latanoprost and bimatoprost-timolol groups at Week 2 ([redacted] and [redacted], respectively), Week 6 [redacted] and [redacted],

respectively) and Month 3 [redacted] and -[redacted], respectively), with no statistically significant differences.

- **Percentage of participants achieving pre-specified mean, mean change and percent mean change diurnal IOP levels at each post-treatment timepoint (ITT population):** There were no statistically significant differences between the groups regarding achievement of pre-specified mean IOP, IOP reduction from baseline or percent reduction from baseline of IOP.

Health-related quality of life (HRQoL): change in Short Form Health Survey Questionnaire 36 score

HRQoL was reported using the Short Form Health Survey Questionnaire 36 (SF-36) score. Scores are reported in Document B, Table 13 of the CS. Mean scores were similar across groups with no statistically significant differences for most of the subscales. Mean change between baseline and Month 6 was also not statistically significant for either group.

3.2.3 Subgroup analyses

Subgroup analyses of MERCURY 3 were based on age, gender, race, iris colour, maximum baseline IOP value, prior hypotensive medication and country. The ITT population was used, including observed data only. Results showed that the netarsudil-latanoprost and bimatoprost-timolol groups were generally similar for specified subgroups.

3.2.4 Adverse events in MERCURY 3

Adverse events were more common in the netarsudil-latanoprost group than the bimatoprost-timolol group. The company presents details of adverse events in the MERCURY 3 trial in Document B, Section B.2.10 of the CS. The safety population was defined as all randomised participants who received at least one dose of study medication. Mean exposure was [redacted] in the netarsudil-latanoprost group (n=218) and [redacted] in the bimatoprost-timolol group (n=212). An overview of treatment-emergent adverse events (TEAEs) is presented in Document B, Table 27 of the CS, reproduced as Table 8 below.

Table 8 Overall summary of treatment-emergent AEs by treatment group in MERCURY 3 – safety population [reproduced from Document B, Table 27 of the company's submission]

	Netarsudil-latanoprost QD (N = 218), n (%)	Bimatoprost-timolol QD (N = 212), n (%)
Number of TEAEs	483	290
Number of subjects with ≥1 TEAE	[redacted]	[redacted]
Number of ocular TEAEs	352	131
Number of subjects with ≥1 ocular TEAE	131 (60.1)	64 (30.2)
Number of non-ocular TEAEs	131	159
Number of subjects with ≥1 non-ocular TEAE	69 (31.7)	75 (35.4)
Number of serious TEAEs	8	10
Number of subjects with ≥1 serious TEAE	7 (3.2)	7 (3.3)
Number of treatment-related TEAEs*	291	91
Number of subjects with ≥1 treatment-related TEAE*	120 (55.0)	53 (25.0)
Number of treatment-related serious TEAEs*	0	0
Number of subjects with ≥1 serious treatment-related TEAE*	0 (0.0)	0 (0.0)
Number of subjects with TEAEs by maximum severity:		
Mild	64 (29.4)	65 (30.7)
Moderate	74 (33.9)	35 (16.5)
Severe	15 (6.9)	10 (4.7)
Unknown/missing	[redacted]	[redacted]
Number of subjects with TEAEs resulting in discontinuation of test agent	[redacted]	[redacted]
Number of subjects with TEAEs resulting in death	[redacted]	[redacted]

Source: MERCURY 3 CSR;[18] *Treatment-related TEAEs were defined as reported as possibly related to related to the study drug.[19] Abbreviations: QD – Once daily; TEAE – Treatment-emergent adverse event.

A greater proportion of participants in the netarsudil-latanoprost group discontinued study treatment due to TEAEs than the bimatoprost-timolol group. This was reported in Document B, Table 27 of the CS as [redacted] in the netarsudil-latanoprost group and [redacted] in the bimatoprost-timolol group for the safety population. Section B.2.10.7 of

the CS refers to discontinuations of treatment due to TEAE as [redacted] of the netarsudil-latanoprost group for the randomised population. Either way, there was a clear imbalance between groups in the number of discontinuations of study treatment due to TEAEs.

Serious TEAEs were rare, occurring in 3.2% of the netarsudil-latanoprost group and 3.3% of the bimatoprost-timolol group. None of the serious TEAEs were ocular and no individual TEAE occurred in ≥1% of participants in any group.

Ocular TEAEs by system organ class (SOC) occurring in ≥1% of either group are reported in Document B, Table 28 of the CS. A total of [redacted] and [redacted] of the netarsudil-latanoprost and bimatoprost-timolol groups respectively, experienced 'eye disorders', the most common being conjunctival hyperaemia (33.0% and 10.8%), respectively, cornea verticillate (11.0% and 0.0%, respectively), conjunctival haemorrhage (8.3% and 2.4%, respectively), eye pruritis (7.8% and 1.9%, respectively) and punctate keratitis (5.5% and 2.4%, respectively). Of the ocular TEAEs occurring in at least 5% of participants, [redacted] and [redacted] respectively, were rated as severe, [redacted] and [redacted] respectively, as moderate and [redacted] and [redacted] respectively, as mild. Mean duration of resolved conjunctival hyperaemia events was [redacted] days in the netarsudil-latanoprost group and [redacted] days in the bimatoprost-timolol group.

Systemic TEAEs occurring in ≥1% of either group are reported in Document B, Table 29 of the CS. The most frequently reported were [redacted] and [redacted] respectively), [redacted] ([redacted] and [redacted] respectively), [redacted] ([redacted] and [redacted] respectively), and [redacted] ([redacted] and [redacted] respectively).

Treatment-related TEAEs were experienced by 55.0% of the netarsudil-latanoprost group and 25.0% of the bimatoprost-timolol group with the majority being of the eye disorder SOC ([redacted] and [redacted] respectively). Non-ocular treatment-related TEAEs were rare, with none occurring in at least 1% of either group. No serious treatment-related TEAEs were reported in either group.

Overall, the EAG's clinical experts are satisfied that the adverse events reported in the CS are as expected from clinical use of netarsudil-latanoprost in these patients and have no concerns.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Table 1 of the company's clarification response (adapted as Table 9 below) reports a summary of studies identified for inclusion in the NMA following the updated review. Please note that studies only considered for the original submission are not shown.

The EAG noted several close similarities between two trials (Katz et al., 2013[20] and Whitson et al., 2013),[21] but also noted that these had different clinical trial numbers, slightly different numbers of participants and no overlapping authors, although they did share the same medical writer. On balance, the EAG considers the two trials to be distinct sister studies.

Table 9 Overview of studies included in NMA reported by the company at clarification [adapted from Table 1 of the company's clarification response]

Trial name (country)	Intervention/comparator(s) (n analysed)	Participants	IOP endpoints
DuBiner *et al*. (2001)[a] (USA)[22]	[Monotherapy head-to-head] Brimonidine (n=64) vs Latanoprost (n=61)	Bilateral OAG or bilateral OHT (previously treated or treatment naïve) Treatment naïve: Brimonidine: 39.4% Latanoprost: 47.5%	• Mean IOP and mean change in IOP at month 1 and month 3
Nixon *et al*. (2009)[a] (Canada)[23]	[FDC head-to-head: FDC as monotherapy or as adjunctive to a prostaglandin] Brimonidine-timolol (n=91) vs Dorzolamide-timolol (n=89)	Glaucoma or OHT and in need of lower IOP in each eye (untreated or currently on IOP-lowering therapy)	• Mean IOP at month 3
Rigollet *et al*. (2011)[a] (Spain)[24]	[FDC head-to-head] Latanoprost-timolol (n=42) vs Bimatoprost-timolol (n=42) vs Travoprost-timolol (n=44)	Primary OAG or OHT (previously treated with at ≥2 hypotensor drugs)	• Absolute decrease in IOP at month 1, month 2, month 3, month 4, month 5, month 6, and month 12
Katz *et al*. (2013)[a] (USA)[20]	[FDC vs component monotherapies] Brinzolamide-brimonidine (n=209) vs Brinzolamide (n=224) vs Brimonidine (n=216)	OAG or OHT (unclear if previously treated)	• Mean IOP at specified time points at week 2, week 6, and month 3
Whitson *et al*. (2013)[a] (USA)[21]	[FDC vs monotherapies] Brinzolamide-brimonidine (n=218) vs Brinzolamide (n=229) vs Brimonidine (n=232)	OAG or OHT (unclear if previously treated)	• Mean IOP at week 2 and month 3, percentage reduction in IOP from baseline to month 6, absolute IOP reduction from baseline to month 6

Trial name (country)	Intervention/comparator(s) (n analysed)	Participants	IOP endpoints
Kozobolis *et al*. (2017)[b] (Greece)[25]	[FDC head-to-head] Brinzolamide-brimonidine (n=22) vs Dorzolamide-timolol (n=22)	Primary OAG (newly diagnosed or previously treated) Treatment naïve: Brinzolamide-brimonidine: 45.5% Dorzolamide-timolol: 40.9%	• IOP at specified time points (morning and afternoon) at week 1, week 4, week 8 and week 12
MERCURY 1[b] (USA)[26]	[FDC vs component monotherapies] Netarsudil-latanoprost (n=238) vs Netarsudil (n=244)* vs Latanoprost (n=236)	OAG or OHT (previous treatment or no previous treatment)	• Mean IOP and mean diurnal IOP at week 2, week 6, month 3, month 9, month 12, and month 13 (off treatment extension period)
MERCURY 2[b] (USA, Canada)[27]	[FDC vs component monotherapies] Netarsudil-latanoprost (n=245) vs Netarsudil (n=255)* vs Latanoprost (n=250) vs	Bilateral OAG or OHT (previous treatment or no previous treatment)	• Mean IOP and mean percentage change in IOP at week 2, week 6, and month 3
MERCURY 3[b] (Austria, Belgium, Czechia, France Germany, Hungary, Italy, Latvia, Poland, Spain, UK)[18]	[FDC head-to-head] Netarsudil-latanoprost (n=218) vs Bimatoprost-timolol (n=212)	OAG or OHT in both eyes (previously treated)	• Mean IOP at specified time points at week 2, week 6 and month 3

Abbreviations: IOP – Intraocular pressure; US – United States; OAG – open angle glaucoma; OHT – ocular hypertension
*Treatment arm not included in the assessment – monotherapy does not bridge the network.
[a]Quality assessment not reported by the company; [b]Quality assessment reported in original submission

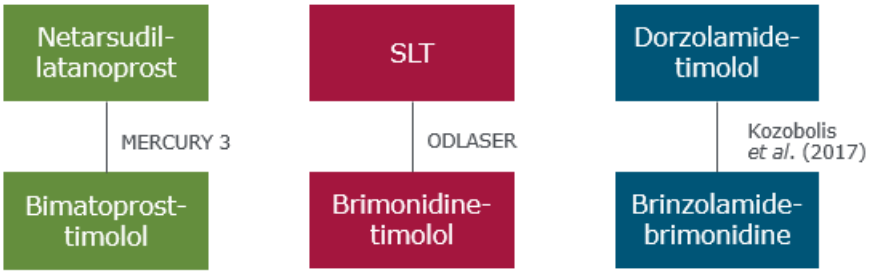
3.4 Critique of the indirect comparison and/or multiple treatment comparison

As MERCURY 3 was the only trial comparing netarsudil-latanoprost against another FDC, the company attempted to conduct indirect treatment comparisons. This was done in two phases. In their original submission (June 2023) the company presented two population-adjusted indirect comparison approaches. Following feedback from the EAG during clarification and a subsequent extension granted by NICE, the company submitted new analyses in October 2023 using a network meta-analysis (NMA) approach.

3.4.1 Unanchored approaches to indirect treatment comparisons

The matching-adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) methods are two approaches for population-adjusted indirect comparisons (using propensity score and regression approaches respectively) that can be used to reweight data in the situation where individual participant data (IPD) are available for one study but only aggregate published data are available from other studies. Anchored indirect comparisons may be used when there each trial has a common comparator arm, otherwise unanchored comparisons must be used.

Figure 3 shows the three studies used by the company in these analyses. IPD from MERCURY 3 (comparing netarsudil-latanoprost versus bimatoprost-timolol) was used alongside published data from two other randomised trials comparing selective laser trabeculoplasty (SLT) versus brimonidine-timolol and dorzolamide-timolol versus brinzolamide-brimonidine respectively.[25, 28] As these treatments were not directly connected to a network containing netarsudil-latanoprost, anchored population-adjusted approaches were not possible. It was, however, possible to consider unanchored methods, although these have very strong assumptions, including that all effect modifiers and prognostic variables are known and adjusted for.[29]



Abbreviations: SLT – Selective laser trabeculoplasty

Figure 3 Unanchored indirect treatment comparisons evidence network (reproduced from Figure 10 of the original company submission)

The company's analyses compared netarsudil-latanoprost with the three fixed-dose combination (FDC) treatments from these studies. It is not clear why further treatments were not evaluated.:

- Netarsudil 0.02%/latanoprost 0.005% FDC (IPD available from MERCURY 3)[18]
- Brimonidine 0.2%/timolol maleate 0.5% FDC (published data from ODLASER)[28]
- Dorzolamide 2%/timolol 0.5% FDC (published data from Kozobolis et al. 2017)[25]
- Brinzolamide/brimonidine FDC (published data from Kozobolis et al. 2017)[25]

The outcome chosen for these analyses was percentage reduction from baseline in diurnal IOP. Analyses were proposed for two other outcomes, but this was not possible due to data limitations.

The company first conducted a feasibility assessment to check the appropriateness of conducting an unanchored approach and stated that population differences between studies supported the need for a patient-adjusted indirect comparison. In particular, one study recruited treatment-naïve patients only.[25]

3.4.1.1 Unanchored MAIC

In this analysis a logistic propensity score model was developed using data from MERCURY 3. Due to data limitations only two of the variables considered critical or beneficial for inclusion could be included. These were age and IOP at baseline. Several other variables that were identified by a clinical expert as being important for

inclusion were not available. These included cup to disc haemorrhages, visual field mean deviation, retinal nerve fibre layers and corneal hysteresis.

The effective sample size for each treatment in the analyses was reduced from [redacted] (the unweighted sample size in MERCURY 3) to [redacted], [redacted] and [redacted] in the brimonidine-timolol, brinzolamide-brimonidine and dorzolamide-timolol analyses, respectively. This large reduction in effective sample size suggests potential issues that could affect the reliability of these analyses. For these reasons the company state that the MAIC approach may not be optimal for the submission. The EAG agrees with this assessment. As they have not been able to justify that all relevant effect modifiers and prognostic variables have been controlled for, there is potential for an unknown amount of bias that may be larger than the treatment effect.

3.4.1.2 Simulated treatment comparison (STC)

The STC method uses a regression approach for population adjustment. Once again, this was only performed for a single outcome: mean percentage change in diurnal IOP from baseline. Although mean percentage change in IOP was available in the relevant publications, standard errors or standard deviations were not available and had to be imputed. As before, due to the limited availability of data adjustment could only be made for two covariates.

Although the company point out that, unlike MAIC, STC analyses are not affected by a reduced effective sample size and that there is precedent in using these analyses in a previous STA, they do not provide a particularly strong case for this approach. As previously, the STC method assumes that analyses are adjusted for all effect modifiers and covariates and there is no assessment of the impact of only controlling for age and baseline IOP. There are also important population differences between studies but little discussion of which target populations the results would be valid for.[29]

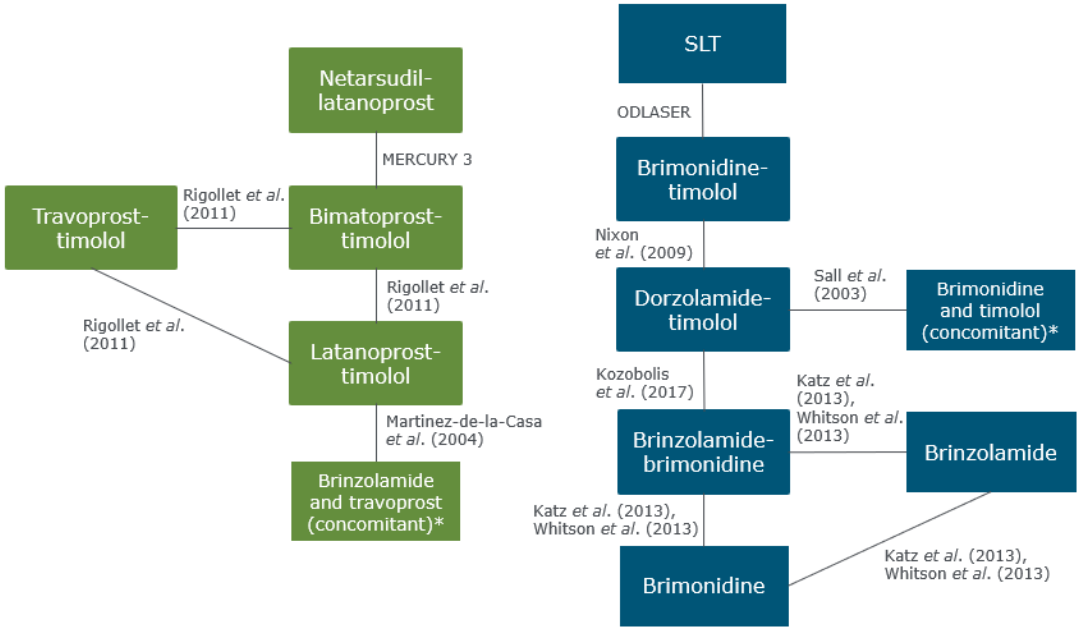
Therefore, the EAG believes that many of the limitations of the MAIC approach also apply to the STC approach and suggests that the NMA methods used in the updated submission should be considered instead, although, there are also methodological challenges in implementing this kind of approach.

3.4.2 Network meta-analysis (NMA)

The company did not present the results of a NMA in their original submission. Although four randomised trials were deemed eligible, they did not form a connected network of treatments. Netarsudil-latanoprost was originally part of a connected network of four treatments incorporating MERCURY 3 and one other study (Guven Yilmaz et al., 2018),[30] but this trial had a follow-up duration of just 24 hours and was considered not to have any useable data. This left netarsudil-latanoprost disconnected from all treatments except for bimatoprost-timolol and meant that a NMA was not possible.

The EAG advised that a NMA might still be feasible and recommended changes to the search strategy including searching for studies before 2017. It also pointed out that the STC and MAIC approaches had strong assumptions that were difficult to justify. If an updated search still did not result in a connected network, one option would be to include monotherapies in the analysis as specified in NICE's final scope. Following the extension of the clarification process the company submitted the results of a NMA in October 2023.

The search was extended to include pre-2017 FDC studies which increased the number of included trials from three to nine. However, these formed two separate networks that were still not connected (Figure 4): the first involving netarsudil-latanoprost included five treatments and three trials, while the second included seven treatments and six trials.



Abbreviations: FDC – Fixed-dose combination; SLT – Selective laser trabeculoplasty
*Concomitant use (not an FDC)

Figure 4 Updated evidence network, including the FDC clinical studies identified from the targeted database searches [reproduced from Figure 3 of the company's clarification response]

As a single connected network was still not present, the company sought RCTs that compared monotherapies as part of a targeted search. By including MERCURY 1,[26] MERCURY 2[27] and one other trial (DuBiner et al., 2001)[22] a bridge was found to connect the two networks.

However, the process to identify these trials was not systematic. The EAG has identified other possibilities that connect the two networks using monotherapies. This lack of completeness in including monotherapy studies has the potential to introduce bias into the NMA results, particularly for treatments on the right-hand side of the network diagram that are only connected to netarsudil-latanoprost through this bridge.

After bridging the networks, a connected network of 13 treatments and 12 trials was formed. Following the advice of an external statistical expert, the company removed three trials that were considered "dead-end" treatments within the network and would not affect the efficacy estimates. This left a network of ten treatments and nine trials (Figure 5). However, this has not been consistently applied as other "dead-end" treatments remain part of the network. The final network consists of a chain of

treatments with a loop at either end. This means that comparisons of netarsudil-latanoprost against most of the other nine treatments can only be achieved through a single path as there are no loops. This reduces the benefit of the NMA approach in this situation.

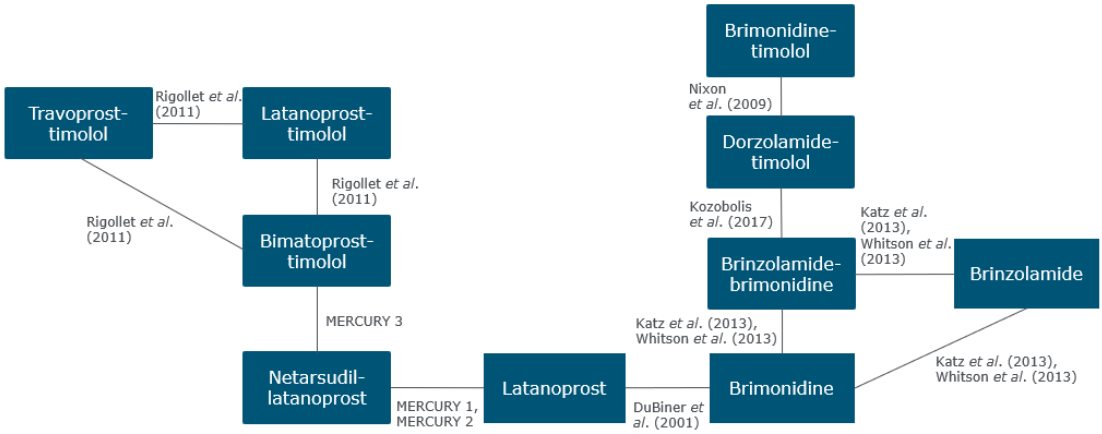


Figure 5 Restricted evidence network for assessment [reproduced from Figure 5 of the company's clarification response]

The company conducted a feasibility assessment for the conduct of an NMA. They concluded that included trials had generally similar study designs and inclusion criteria, although one study[25] only included patients with POAG, whereas the others included both OAG and OHT. There were also large variations in the rates of previous treatment, but there was minimal variation in the treatment doses and regimens. All studies included IOP as an outcome measure, but the definition varied.

The company's analyses followed the recommendations in NICE DSU TSD2 with a random effects model as the main analysis.[31] The EAG considers the methodology used to be appropriate.

There were various complications when deriving the data for the NMA. As well as being measured at different time points post randomisation, IOP was often measured at different times of day (e.g., for Katz 2013 this was at 8am, 10am, 3pm and 5pm).[20] For these studies the mean of all diurnal IOP values was used with the standard deviation estimated as the mean of the SDs for the different times. One study did not report SDs, so these were imputed from other studies in the review.

A further issue was that the company chose to define the NMA outcome as **percentage change in IOP from baseline**, even though this was not always reported in the individual studies. To calculate the percentage change in IOP and its SD, simulations had to be conducted for some studies to estimate the mean percentage change from reported data at baseline and follow-up. A correlation of 0.5 was assumed in this calculation but no reference was provided to justify this assumption.

When conducting the NMA vague prior distributions were used except for the between-study SD of treatment effects. For this an informative prior distribution using a reported value for pharmacological versus pharmacological interventions for odds ratios,[32] which was then converted to a mean difference scale using the method of Ren et al., 2018.[33] The justification for this approach is not clear and the EAG is unclear about how robust this will be in practice. A non-informative prior would have been acceptable as the NMA results are unlikely to be sensitive to the starting values.

The NMA provided treatment effects for percentage change in diurnal IOP for netarsudil-latanoprost versus the nine other treatments in the network. None of these effects were statistically significant (i.e., the 95% CrI always included zero) and the CrIs were wide suggesting uncertainty (Figure 6). The results were similar regardless of whether a fixed or random effects approach was used. The company used the fact that all effects were close to zero to argue that there were negligible differences in treatment efficacy between all therapies considered.

Abbreviations: IOP – Intraocular pressure; SD – Standard deviation
To achieve convergence, the burn-in was 100,000, with 50,000 iterations kept. The analysis was run with a thinning interval of 30.

Figure 6 Forest plot of percentage change in diurnal IOP from baseline (random effects model) [reproduced from Figure 6 of the company's clarification response]

The 95% CrIs for these analyses seem very wide. For example, for Figure 6 the company made it clear that when multiplied by 100 the results represent a difference in percentage change in diurnal IOP between baseline and follow-up. The first result would be interpreted as netarsudil-latanoprost having a reduction of mean diurnal IOP that was [redacted] percentage points lower than brimonidine-timolol, with a 95% CrI that ranged from [redacted] points lower to [redacted] points higher. Unfortunately, the company did not supply a table of mean percentage change by study arm that would have allowed the EAG to check the consistency of these results.

The company then states that the NMA results indicate that all treatments have similar efficacy because no results were statistically significant and "*the hypothesis of no difference is central in the credible intervals of all comparisons with netarsudil-latanoprost*." They go on to state that, "*it can be concluded that there is no difference in treatment effect between the different treatment strategies*." The EAG is uncomfortable with this statement – the wide CrIs indicate considerable uncertainty including differences in percentage change in IOP that might be considered clinically important – and notes that this uncertainty does not appear to have been explicitly accounted for in the cost-effectiveness modelling.

3.5 Additional work on clinical effectiveness undertaken by the EAG

None

3.6 Conclusions of the clinical effectiveness section

The EAG had several concerns about the clinical effectiveness evidence.

These included concerns about the scope and completeness of the searching process for the original review which only identified FDC studies published between 2017 and 2022. However, in the updated review this was extended to cover all relevant studies.

The company amended NICE's scope to exclude topical monotherapies and surgeries such as SLT as comparators. The EAG's clinical advisers agree that it makes sense to compare netarsudil-latanoprost only against other therapies at the same stage on the treatment pathway. However, this was not always implemented consistently.

SLT was included in the NMAs for the original and updated reviews. For the original systematic review, this seemed to be only because the comparator in the ODLASER trial was included in the unanchored analyses. In the updated review SLT and two concomitant monotherapy regimens (brinzolamide and travoprost, brimonidine and timolol) were included in the network diagram before being dropped for reasons that were not clearly stated. The study by Guven Yilmaz et al., 2018 was only included in the network diagram for the original submission, although this study had no useable data.

Use of percentage change in diurnal IOP as the primary outcome definition

The EAG's clinical advisers agree that the most clinically relevant definition of the IOP outcome is percentage change from baseline in mean diurnal IOP. However, because only some studies reported useable data relating to percentage change, using this outcome definition results in additional uncertainties in the calculation of treatment effect estimates than would be the case if they had chosen to use mean IOP at three months, a definition used in other systematic reviews in this area.[34] In the company's submission data manipulation was often required as publications did not always report IOP in the required format. In addition to needing to average results from different times of day and to impute of SDs from other studies, for some studies the company had to use simulations to derive useable data.

Because of these issues the EAG would have liked to have seen a data table of percentage change in mean diurnal IOP used for each study in the NMA following manipulation of data. This was not supplied within the clarification response. If included, this would have enabled the EAG to gauge whether the reported NMA results had face validity.

Original review using unanchored methods

The EAG had important concerns about the original indirect treatment comparison analyses presented. The unanchored methods to compare netarsudil-latanoprost to other comparators (MAIC and STC) have strong untestable assumptions that are difficult to justify in this situation. The company's preferred approach of STC requires that analyses are adjusted for all effect modifiers and prognostic variables, but the lack of suitable data meant only age and baseline IOP could be included as covariates. This means that results from these analyses could be subject to bias of unknown magnitude and may not be reliable.

Updated analyses using network meta-analysis (NMA)

In the updated review, selected monotherapy studies were included to enable a connected network for an NMA. The main drawback of this approach is that the linking studies[22, 26, 27] were not selected using an objective systematic process and there are other possible paths that would connect the two sides of the network diagram.

The EAG agrees with the decision to expand the search to include trials conducted prior to 2017. The EAG also suggested that monotherapies could be used to bridge between a disconnected network of FDC trials, although they were not aware that this would be a major undertaking because of the very large number of published monotherapy trials. However, they had assumed that any new analyses would be done according to the general principles of systematic reviews. The company's updated analyses are vulnerable to bias because of the *ad hoc* way in which monotherapy trials were selected for inclusion. Furthermore, as the resulting network resembled a chain of trials with only two loops, effect estimates are likely to be less robust than if all monotherapy trials had been included to form a web of treatments,

and this is particularly the case for comparisons with treatments on the opposite side of the diagram to netarsudil-latanoprost.

An alternative approach would be to include one or more monotherapies as comparators in a full systematic review, but the EAG's initial searches indicate that many trials would have been eligible and the delivery of a full NMA would have been difficult to achieve in the time scale of the NICE submission process. Additionally, most of the network would then be populated with evidence from monotherapy trials that may not be considered on the same part of the treatment pathway as netarsudil-latanoprost and other FDCs.

The EAG accepts that there is no easy option for the conduct of an appropriate analysis in the time available, but as a minimum would have liked to have seen sensitivity analyses exploring different ways of linking the two disconnected networks to see if they provided similar results. Alternatively, a subset of monotherapy trials could have been included based on pre-specified criteria such as by year of publication or other criteria agreed with clinical experts. The EAG recommends that the current NMA results should only be used with caution, accounting for the wide credible intervals of the estimates obtained and accepting that there may be additional bias or uncertainty in these estimates.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature search to identify cost-effectiveness studies of treatments for adults with ocular hypertension (OHT) or primary open angle glaucoma (POAG). Searches of databases were for studies published from 2017 onwards, up to a cut-off date of November 2022. Details of the company's original literature search for cost-effectiveness studies can be found in Appendix G of the CS. Two studies were identified, as summarised in Table 36 of the original CS. One of those studies included a Markov cohort decision analysis model of glaucoma disease progression over a lifetime horizon. The study showed that SLT dominated eye drops.[35]

The EAG is satisfied that the search strings for the post-2017 search of economic evaluation studies is comprehensive. However, the EAG considered the restriction of literature searches to post-2017 to only be a partial assessment of the cost-effectiveness evidence base for OHT and POAG treatments. Given that the company have used a decision model for the current assessment that does not capture glaucoma disease progression over time, the EAG considers it important to understand the existing economic evaluation evidence base to consider the appropriateness of the company's chosen modelling approach (see Section 4.2.2). At clarification stage, the EAG suggested several studies in the literature that had not been captured by the company's original review. The EAG also identified a systematic review of cost-effectiveness studies and suggested that the company consider the appropriateness and relevance of the included studies when constructing their own economic model.[36]

Furthermore, the EAG is concerned that the assessment of inclusion and exclusion criteria for the economic modelling studies may be too narrow to capture all relevant information for informing an appropriate model structure. For example, cost-effectiveness studies were excluded if the type of glaucoma was not reported. Whilst the company's approach is in line with their stated objective in the original CS, it is

unclear whether additional relevant studies would have been retrieved if the scope of the economics searches was widened to capture all glaucoma studies.

In summary, the EAG was not satisfied that the initial literature search provided a sufficient assessment of the evidence base for the cost-effectiveness of glaucoma treatments more generally, or specifically treatments for OHT or POAG.

Following discussions at the clarification call, the company conducted a further targeted literature search for cost-effectiveness studies published prior to 2017. Updated search strategies are provided in Appendix A of the company response to clarification queries. Following a screening process, 18 additional publications were included, leading to a total of 20 cost-effectiveness studies identified from the original and (post-2017) and updated (pre-2017) targeted searches. These include seven studies in the UK. The modelling approach of the additional 18 studies in terms of IOP is described in Appendix A, Tables 59 and 60 of the company response to clarification questions. The initial 2 studies are described in Table 26 in Appendix G of the original submission.

Similarly, to the issues raised in the Chapter 3 critique, the EAG note that the review of cost-effectiveness studies was also targeted, and not systematic. As such, some relevant studies may have been missed during the company's screening processes. Despite these concerns, the EAG is satisfied that the revised literature search provides enough studies from which to inform an appropriate model structure for the current assessment.

The EAGs main concern is that the existing literature base has been inappropriately used to justify a model structure for the assessment that is focused on short term changes in IOP, rather than linking changes in IOP to longer-term risks of conversion from OHT to OAG or for OAG disease progression. The company have provided details of several studies which they claim support or refute the use of their chosen model structure, claiming that most studies support the use of changes in IOP as model health states. It is unclear to the EAG how the studies in Table 12 were identified and selected. Some of the studies appear to be cost-effectiveness analyses, economic models, but others are literature reviews and guideline documents.

Furthermore, the EAG disagrees with the company's assessment of how the reported IOP thresholds in the quoted economic evaluation studies in Table 12 of the response document support their chosen model structure. The EAG considers it more appropriate to consider the relevance of all the economic evaluation studies identified in the company's updated review and how they match the NICE reference case. The company has not provided an assessment of the relevance of all the retrieved economic evaluation studies, and it is unclear how economic evaluation studies were selected for inclusion in Table 12. The EAG has, therefore, provided a revised assessment of the relevance of the economic evaluation studies identified in the company's updated review to the current decision problem in Table 10 below.

Table 10 EAG summary of existing cost-effectiveness studies from company's literature reviews

Study (Author, year)	*Study type (decision model / within trial analysis)*	*Country*	*Population*	*Intervention*	*Comparator*	*Modelled health states (if applicable)*	*Model time horizon (if applicable)*	*EAG assessment of appropriateness of model structure and time horizon*
Gazzard 2019[35]	Markov state transition model	UK	Patients with OAG or OHT	SLT	Eye drops	OHT Mild Glaucoma Moderate Glaucoma Severe Glaucoma Dead	Lifetime	*EAG considers both the model structure and time horizon to be relevant.*
Peeters 2012[37]	Decision tree: covers the first 15 months of therapy Markov model: covers the lifelong follow-up.	Netherlands	Patients with POAG	Latanoprost	Timolol	**Decision tree:** ≤21 mmHg; >21 mmHg and >20% reduction; >21 mmHg and <20% reduction. **Markov model:** Glaucoma; Blindness Death	Lifetime	*The model structure is relevant as it captures the impact in IOP changes on glaucoma and risk of blindness, but additional Markov states may be required to capture different stages of glaucoma progression*
Wickstrom 2010 [38]	Unclear	Multiple European countries	Patients with OAG	Bimatoprost-timolol fixed-combination	Latanoprost-timolol fixed-combination	>15% reduction in IOP; > 20% reduction in IOP	3 months	*Time horizon too short, only relevant is considering costs and assuming equal effectiveness*
Orme 2012[39]	Markov model	UK	Mild to moderate POAG or OHT	Latanoprost monotherapy	Bimatoprost Travoprost	OH: no VFD; Mild Glaucoma Moderate Glaucoma Severe glaucoma	10 years	*Model structure is appropriate, but the EAG disagrees that the utility values are transferable to*

Study (Author, year)	***Study type (decision model / within trial analysis)***	***Country***	***Population***	***Intervention***	***Comparator***	***Modelled health states (if applicable)***	***Model time horizon (if applicable)***	***EAG assessment of appropriateness of model structure and time horizon***
						Blindness		*the company's model structure.*
Stewart 2008[40]	Markov model	USA	Patients with OHT	OHT treatment (not specified)	No treatment	Stable OHT Glaucoma	5 years	*Partly relevant, captures longer term disease, but time horizon too short to capture all relevant costs and benefits*
Rouland 2003[41]	Decision tree	France, Italy, Portugal, Spain	POAG and/ or OHT	Brinzolamide	Dorzolamide	**Decision Tree** treatment response non-response (incorporates treatment switching)	3 Months	*Time horizon not aligned with NICE reference case but may give an indication of relevant costs over short term. Requires an assumption of equal effectiveness*
Lin 2014[43]	Decision-analytic model	Unclear	Patients with OH or POAG	Bimatoprost, latanoprost, tafluprost and travoprost, as first-line monotherapy	NR	NR	1 month	*Insufficient information to judge relevance as not a peer reviewed publication*
Van Gestel 2014[46]	Patient level discrete event simulation model	Netherlands	Patients with OHT, initial IOP of 25mmHg or above	Direct pressure lowering treatment for OHT (timolol)	'Watchful waiting' (treatment postponed until progression	Model events included ophthalmologist visit, conversion to POAG and death;	Lifetime (mean: 26 years); results also reported over 10 years	*The model structure is relevant and describes one approach in which IOP can be used to inform conversion from OHT to POAG.*

Study (Author, year)	*Study type (decision model / within trial analysis)*	*Country*	*Population*	*Intervention*	*Comparator*	*Modelled health states (if applicable)*	*Model time horizon (if applicable)*	*EAG assessment of appropriateness of model structure and time horizon*
					to glaucoma).	(Incorporates a HR for IOP of 1.09 per mmHg higher)		
Van Gestel 2012[47]	Patient-level discrete event simulation model	Netherlands	Patients with POAG	Four different treatments/ monitoring-strategies	Usual care	Several disease progression events informed by IOP, age and other risk factors	Lifetime	*The model structure is relevant and describes one approach in which IOP can be used to inform POAG progression*
Blaser 2011[51]	Decision model (type unclear)	USA	Patients with OAG or OHT	Different dosing for bimatoprost latanoprost travoprost	NR	Multiple lines of treatment following response or failure (definition unclear)	1 year	*Insufficient information to judge relevance as this is a conference abstract only.*
Bernard 2003[37]	Monte Carlo simulation model (type unclear, appears to be Markov cohort)	France	Patients with OAG or OHT	Latanoprost	Beta-blocker	Multiple lines of treatment success / failure, followed by surgery	3 years	*Time horizon too short; partially captures long term outcomes indirectly by modelling multiple lines of treatment*
Cottle 1988[38]	Within trial cost-effectiveness analysis	Canada	newly diagnosed POAG	Pilocarpine; timolol; dipivifrin	NR	N/A	1 year	*Time horizon too short; Treatments not applicable to current decision problem;* *Not a decision model*
Kymes 2006[39]	Markov cohort model	USA	Patients with IOP >24mmHg	Different treatment initiation	No treatment	No POAG POAG Unilateral blindness	Lifetime	*Appropriate time horizon, incorporates disease progression and could be*

Study (Author, year)	*Study type (decision model / within trial analysis)*	*Country*	*Population*	*Intervention*	*Comparator*	*Modelled health states (if applicable)*	*Model time horizon (if applicable)*	*EAG assessment of appropriateness of model structure and time horizon*
				strategies based on risk of POAG		Bilateral blindness		*considered as an alternative approach to modelling lifetime costs and benefits of treatment*
Kymes 2010[40]	Markov cohort model	USA	Patients with OHT	Treatment	No treatment	No POAG 5 stages of POAG Bilateral blindness Death	Lifetime	*Appropriate time horizon, incorporates disease progression and could be considered as an alternative approach to modelling lifetime costs and benefits of treatment; IOP not directly linked to model health states*
Marchetti 2001[41]	Decision tree model	USA	Newly diagnosed or untreated POAG or OHT	Brimonidine	Betaxolol	Decision tree incorporates up to five lines of treatment based on response or failure	1 year	*Time horizon insufficient to capture all costs and benefits. Disease progression partially captured through multiple treatment lines*
Rocchi 1997[42]	Decision model (type unclear)	Canada	Patients aged over 65 with POAG	Dorzolamide	Pilocarpine	Simplified clinical model of success or failure, based on treatment discontinuation	10 years	*Model structure does not capture disease progression and is not sufficient to model all relevant costs and outcomes of care.*

Study (Author, year)	***Study type (decision model / within trial analysis)***	***Country***	***Population***	***Intervention***	***Comparator***	***Modelled health states (if applicable)***	***Model time horizon (if applicable)***	***EAG assessment of appropriateness of model structure and time horizon***
Stein 2012[43]	Markov cohort model	USA	Patients aged 60 with mild OAG	PGA laser trabeculoplasty	No treatment	Mild glaucoma moderate glaucoma severe glaucoma Unilateral blindness bilateral blindness Death	25 years	*The model structure sufficiently captures disease progression but a direct link between IOP and disease progression risks is not built into the model*
Holmstrom 2006[44]	Decision tree	France, Germany, Italy, Spain and UK	Patients with POAG	Bimatoprost latanoprost timolol	NR	2 lines of treatment based on success or failure	1 year	*Model time horizon too short for full assessment of costs and benefits. Decision tree structure does not capture disease progression*
Kobelt 1999[45]	Markov cohort model	UK	Patients with newly diagnosed POAG or OHT	New treatments	Current therapy	7 treatment defined states including surgery and laser	2 years	*Model structure partially captures disease progression through treatment escalation, but time horizon is not sufficient to capture all relevant costs and outcomes.*
Hirst 2013[46]	NR	UK	Patients diagnosed with POAG	Bimatoprost-timolol, dorzolamide-timolol	Tafluprost-timolol	NR	Lifetime	*Insufficient details to assess as this was a conference presentation*

Abbreviations: OAG – Open-angle glaucoma; OHT – Ocular hypertension; SLT – Selective laser trabeculoplasty; POAG – Primary open-angle glaucoma; IOP – Intraocular pressure; VFD – visual field defects; N/A – Not applicable; NR – Not reported; PACG – Chronic primary angle closure glaucoma; COAG – Chronic open angle glaucoma

The EAG summary from Table 10 above shows that 8 out of 20 (40%) of the studies included in the company's review were decision models conducted over a lifetime horizon, and thus directly applicable to the NICE reference case of capturing all relevant costs and benefits of treatment. Of those 8 studies, seven use model health states and structures that attempt to capture conversion from OHT to glaucoma and / or glaucoma disease progression (one study could not be assessed as it was only available as a conference abstract). Further critique of the company's model structure is provided in Section 4.2.2.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 11 reports the EAG's assessment of the company submission (CS) against the NICE reference case. The EAG's checks are applied to the company submitted excel model file post-clarification queries.

Table 11 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	**Partly.** The choice of perspective is appropriate. However, the economic model structure precludes the assessment of all direct long-term patient outcomes
Perspective on costs	NHS and PSS	**Partly.** The model structure precludes the assessment of all relevant costs to the NHS (e.g., costs of surgery associated with advanced disease).
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	**Yes**. A fully incremental CUA is provided, but the presentation of results does not allow for easy interpretation. Table headings and labelling were inconsistent. The EAG has updated results presentation to allow for easier interpretation.

Element of health technology assessment	Reference case	EAG comment on company's submission
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	**No**. Whilst a lifetime model horizon is implemented, the model structure does not capture all the important long-term cost and utility implications of reducing IOP because changes in IOP have not been linked to glaucoma disease progression. The economic model structure is therefore insufficient for decision making over a long-term time horizon.
Synthesis of evidence on health effects	Based on systematic review	**No.** A systematic review submitted for the original CS was insufficient as it only included studies published post-2017. An additional targeted literature search was conducted following clarification queries but is not systematic. It also is not a complete assessment of all the relevant literature and excludes monotherapies. The implication is that treatment effects derived from the NMA and used in the economic model are highly uncertain (See Section 3.4). This uncertainty was not fully explored in the economic model probabilistic analyses.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	**Partly.** Health effects whilst on treatment are measured using QALYs, derived from EQ-5D. However, it is assumed that discontinuing treatment does not impact on IOP, or hence QALYs. The EAG considers that there may be QALY benefits of slowing disease progression or avoiding need to move to subsequent lines of treatment that are not captured in the model. As such, the model output lacks face validity. The modelled QALY estimates may only be relevant over a short (maximum 1 year) time horizon where one is interested in the short-term impact of changes in IOP on QoL and the impact of adverse events on QALYs.

Element of health technology assessment	Reference case	EAG comment on company's submission
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	**Yes.** The company has used a mapping algorithm to convert patient reported SF-36 data to EQ-5D for different changes in IOP observed within the MERCURY 3 trial.[18] Scenario analyses requested by the EAG to use SF-6D utilities in the model were not provided and information provided on SF-6D utilities were inaccurate. Scenario analyses applying published utilities for glaucoma health states to health states defined based on percentage changes in IOP from baseline are not appropriate for decision making.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	**Yes.** UK value sets appeared to be used where possible.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	**Yes.**
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	**Partly.** The perspective of costs is in line with the reference case. However, the model structure is inadequate to capture the long-term costs of glaucoma disease progression, meaning that lifetime costs output from the model are unlikely to reflect the costs or resource

Element of health technology assessment	Reference case	EAG comment on company's submission
		use incurred in UK clinical practice over the longer term. The EAG disagrees that it is appropriate to use a mix of NHS indicative prices (branded) and drug tariff prices (generics) for glaucoma treatments. The EAG prefer the use of eMIT prices if treatment is prescribed in secondary care and drug tariff prices from the BNF if treatment is prescribed in primary care. The EAG considers adverse event management resource use to be overestimated with respect to how CTCAE grades 1 and 2 are usually managed in UK clinical practice.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	**Yes.** Discounting of costs and health effects is at 3.5% per annum in line with the NICE reference case. Discounting appears to be correctly implemented in the model.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company developed a four-state Markov model (Figure 14, page 103, Document B, Company evidence submission, reproduced below) based on IOP reduction from baseline (i.e., a) <20%, b) 20% - 30%, and c) >30%), and the absorbing state Death.

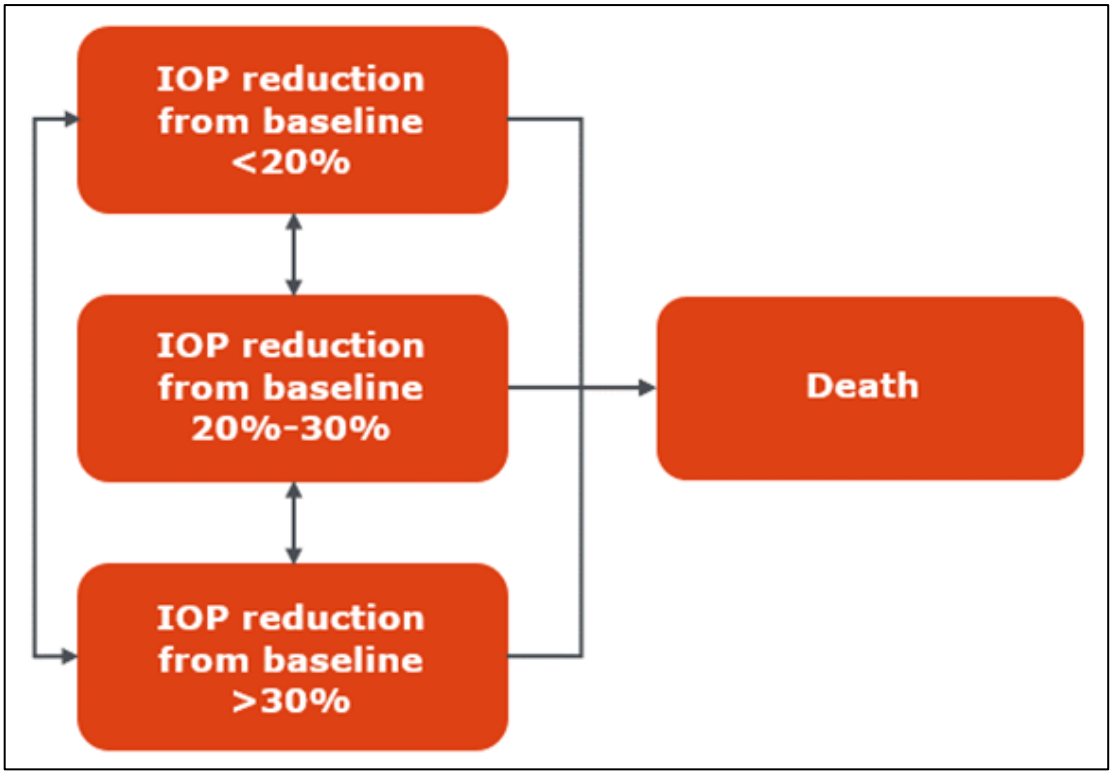


Figure 7 Company's Markov model structure [reproduced from Figure 14, Document B of the company's submission]

Abbreviations: IOP – Intraocular pressure

The EAG does not consider the company's economic model structure to be appropriate to capture all the relevant long-term costs and benefits associated with the impact of improvements in IOP on reducing the time to progression of glaucoma disease. The EAG does not agree with the company's statement that the model structure aligns with NICE guidelines. The NICE NG81 economic model uses an initial decision tree to model the decision on treatment and a Markov model to allow for long term consequences, with Markov states based on glaucoma severity as detailed in NICE NG81.[17] The model health states are described in Table 12 below. Other economic evaluation studies assessing the cost-effectiveness of treatment for glaucoma, such as the LiGHT study by Gazzard et al. 2019 and referenced by the company, also used a model structure similar to the structure used in the NICE guidelines model.[35]

Table 12 NICE glaucoma model COAG staging [reproduced from NICE NG81 Table 30, Appendices document, page 411]

COAG stage	Mean defect (MD) score
No COAG (a)	*No visual field defect*
Early	*-0.01 to -6.00 dB*
Moderate	*-6.01 to -12.00 dB*
Advanced	*-12.01 to -20.00*
Severe Visual Impairment (SVI)	*-20.01 or worse*

(a) Includes OHT patients

At clarification questions, the EAG asked the company to re-structure the model to capture the impact of changes in IOP on glaucoma disease progression suggesting that such a model could include health states defined by, for example, mild, moderate and severe disease.

The company have chosen not to amend their model structure as requested and have instead relied on their interpretation of the literature to justify the approach taken. The EAG continues to disagree that a model based on changes in IOP alone is appropriate to assess long-term costs and benefits of treatments. A model structure, similar to that requested by the EAG, has been used by several existing studies included in the company's literature review and summarised in Table 12 of the company's response to clarification queries. Further details of the EAG's assessment of the appropriateness of existing economic evaluation model structures for the current decision problem are provided in Table 10, Section 4.1 above.

The company further stated that the "*choice of a Markov state transition cohort structure and the use of IOP to define health states was validated by a UK clinical expert*".

The EAG understands that reduction of IOP level is a surrogate outcome for OHT and glaucoma treatment success, as the level of IOP is the only risk factor for conversion to glaucoma and glaucoma progression that can be modified. The EAG understands that, whilst the reduction in IOP is an important outcome in the

treatment of OHT and glaucoma, the final aim of reducing IOP is to avoid vision loss and the associated quality of life reduction and additional treatment costs. The EAG does not agree with the company statement that the health states defined in the company's model reflect the long-term goals of OHT and glaucoma treatment. The long-term goal of treatment is to preserve visual function as visual function is a key element affecting quality of life (utilities). In the company's model structure changes in IOP are not linked to glaucoma conversion or disease progression. A model schematic for the long-term effects of glaucoma similar to those used in the NICE guideline NG81[17] and the LiGHT trial by Gazzard et al. 2019[35] is presented below. To note, no backward transitions are possible for glaucoma conversion or glaucoma progression.

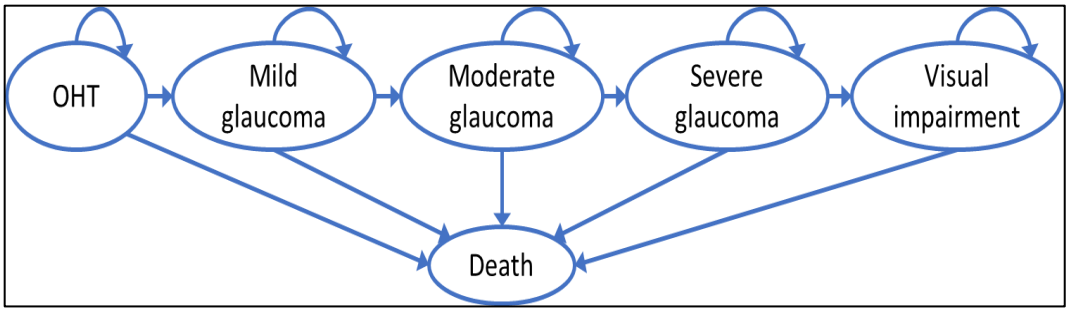


Figure 8 EAG suggested model structure.

Glaucoma is a chronic condition and the vision loss due to glaucoma severity is irreversible. The EAG understands that, in a glaucoma model, long term health related quality of life should be primarily associated with the vision loss and severity of glaucoma. The model long-term utilities should reflect the fact that glaucoma damage and vision loss due to glaucoma is irreversible, and modelled individuals should not be able to 'recover' utility. The company model allows transitions between any of the three model non-Death states (i.e., IOP reduction from baseline less than 20%, 20 to 30% and >30%) that are associated with different utility levels. Therefore, modelled individuals can move to states where they enjoy higher quality of life. As quality of life follows disease severity (i.e., vision loss), the EAG understands the company model implicitly assumes that the vision loss due to glaucoma is reversive. The EAG does not agree with this implicit assumption. We expand on the utility implications in section 4.2.7 Health related quality of life.

4.2.3 Population

The company's economic evaluation includes adult patients diagnosed with either POAG or OHT in both eyes for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction. The starting mean age (67.2 years) of cohort used in the model was obtained from the full trial population from the MERCURY 3 trial. The company state that the target population aligns with the approved marketing authorization for the combination of netarsudil and latanoprost[47] and the population studied in the MERCURY 3 trial.[18]

The EAG has cross-checked the model population with the marketing authorisation and are satisfied that these are aligned. The EAG's clinical expert agrees that the modelled population are broadly representative of the people who would receive FDC therapies in UK clinical practice.

The company original submission explains that the MERCURY 3 study included patients with OHT and POAG, whilst most studies from their literature review for the indirect comparison related to POAG only. The company state that a scenario analysis is provided that aligns the populations between the MERCURY 3 and comparator trials in the ITC when calculating relative treatment effects, by removing OHT patients from the MERCURY 3 patient-level data. Implementing this scenario did not impact the transitions for netarsudil-latanoprost or bimatoprost-timolol – only the remaining FDC comparators.

The EAG are unclear as to how this analysis has been implemented, and whether it impacts on transition probabilities in the model. The EAG further notes that this scenario analysis was not provided using the company's updated post-clarification economic model. Post factual accuracy check, the company clarified that it was not possible to provide this scenario because it was not possible to match patient level data in the NMA. The EAG consider this an important consideration and would appreciate additional scenario analyses exploring the impact on cost-effectiveness of patients with OHT or POAG. If the model structure was developed to align with the disease pathway, it would be straight-forward to conduct scenario analyses varying the starting populations in the model and / or applying subgroup specific transition

probabilities. It is unclear how meaningful subgroup analyses of OHT / POAG would be in the current model configuration.

The original company submission was unclear as to whether the modelled population related to the 'best' or 'worst' seeing eye. In the MERCURY 3 study, one eye was selected as the 'study' eye and one as the 'fellow' eye. Only 'study' eyes were evaluated for all the efficacy measures, even though treatment was administered to both eyes. The fellow eyes were independently evaluated. Following clarification, the company explained that in the MERCURY 3, all patients (100%) were treated in both eyes, though the primary economic analysis focused on the 'study eye,' without pooling data for both eyes. They noted that a previous pharmaceutical company, Aerie®, conducted the MERCURY 3 study and wrote the clinical study report (CSR). At the factual accuracy check stage for the assessment, the company provided additional clarification and evidence. The Stalmans et al. 2023 publication clarifies that the selection of study eye was dependent on the eye with the higher IOP (the worst seeing eye). In response to clarification, the company added a switch to the economic model to allow transition probabilities to follow either the 'study' ('worst seeing') or 'fellow' ('best seeing') eye.

The EAG accepts the additional clarification provided by the company. The EAG note that uncertainty remains because costs are likely to follow the 'worst' seeing eye, with quality of life likely to follow the 'best' seeing eye. Furthermore, when applying the switch to the 'fellow' (assumed) best seeing eye, the costs increase slightly and QALYs decrease slightly relative to the base case (study eye). Although the magnitude of impact is small, the EAG are concerned that this output may lack a degree of face validity when assessed against what might be expected in clinical practice. It is feasible that the lack of model face validity output is a consequence of other issues raised with regards to treatment effectiveness and model structure throughout this report.

In relation to the remaining comparators, not included in MERCURY 3, the company clarified that the studies included in the NMA did not report the proportion of patients that received treatment in one or both eyes (See Table 45 of the clarification response document). They further explained that national guidelines are also inconsistent with

recommendations to treat one or both eyes,[14] but that the summary of product characteristics for brinzolamide and travoprost, netarsudil-latanoprost, bimatoprost and timolol, and brimonidine and timolol all mention using the product in the affected "eye(s)", suggesting treatment of both eyes is common practice.

The EAG's clinical experts are satisfied that both eyes are typically treated in UK clinical practice. The EAG is therefore satisfied that the inclusion of both eyes in the model is appropriate for decision making and it is appropriate to conduct sensitivity analysis around best and worst seeing eyes. Whilst the ideal model would allow costs to follow the 'worst-seeing' eye, with QoL following the 'best-seeing' eye, the EAG appreciate that this may be difficult to accurately model and that there are more important concerns with the model structure overall.

The EAG also note that the included studies in the NMA do not accurately identify whether the study eye is best or worst seeing. An inability to identify which eye is contributing data to the NMA further increases uncertainty in modelled incremental costs and QALYs, particularly for the treatments not included in the MERCURY 3 trial. The magnitude and direction of any bias is unclear.

4.2.4 Interventions and comparators

The modelled intervention is latanoprost 0.005%, ophthalmic solution and netarsudil mesylate 0.02%, provided as one drop in the affected eye(s) daily in the evening. The fixed dose combination therapy is marketed as Roclanda. There are no dosing adjustments and patients are modelled to remain on treatment indefinitely, only discontinuing treatment at a rate and for reasons observed in the MERCURY 3 trial (primarily adverse event related discontinuation).

The modelled comparator from the MERCURY 3 trial is bimatoprost-timolol, consisting of bimatoprost 0.03% and timolol maleate 0.5% ophthalmic solution, taken as one drop daily in the affected eye(s). The FDC is marketed as Ganfort. The dosing details and assumptions for the remaining seven comparators are detailed in Table 52 of the original submission.

The EAG is satisfied that the model dosing of netarsudil-latanoprost and bimatoprost-timolol is consistent with the dosing in the MERCURY 3 study and the marketing authorisation for the respective treatments. Upon further investigation of the model file and references, the EAG is also satisfied that the dosing of the remaining seven comparators is in line with the summary of produce characteristics for those treatments. The EAG's clinical expert confirms that the dosing of netarsudil-latanoprost is as would be anticipated in UK clinical practice.

4.2.5 Perspective, time horizon and discounting

The company's model includes costs from a UK NHS perspective. Social care costs were not explicitly considered in the model.

The EAG view is that there may have been relevant social care costs to consider if the company adopted a decision modelling structure that captured the lifetime impact of glaucoma disease progression, up to and including loss of sight.

The model was run for a time horizon of 33 years, from a starting age of 67 up to age 100. The company's original submission states that a lifetime horizon was chosen to enable "disease progression to be monitored over a patient's lifetime".

The EAG agrees that a lifetime horizon model is required to assess the incremental cost per QALY for netarsudil-latanoprost, compared to other FDC treatments. However, the company's current model structure does not capture the full lifetime impact of glaucoma on costs and outcomes (See Section 4.2.2). The EAG is satisfied that costs and benefits are accrued in the economic model over the stated time horizon but note that the model traces are configured to run for a maximum of 40 years overall. Therefore, any exploration of starting ages less than 60 should be interpreted cautiously. Indeed, some of the samples drawn from the probabilistic distribution for age would include values less than 60. However, the impact of this in terms of biasing cost-effectiveness results is likely to be minimal.

The company's model includes discounting of costs and QALYs at 3.5% per annum.

The EAG is satisfied that the company's discounting approach is consistent with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness

Overview and context:

The EAG's critique of the company's approach to modelling treatment effectiveness should be read in conjunction with the concerns raised regarding the economic model structure. The ideal model structure would use a glaucoma disease progression model, with health states for OHT, mild, moderate, and severe glaucoma. The impact of changes in IOP on model transition probabilities should be derived based on key risk factors including starting health state (OHT or various severity of glaucoma), the impact of IOP on disease progression, and the underlying risk factor of age. These risk factors should have been used in a linked evidence approach to map the treatment effect sizes on change in IOP from baseline to subsequent glaucoma disease progression. There are several examples of how this can be achieved in the published literature, including the company's own systematic review of economic evaluation studies. Given the impact of concerns around the model structure, the EAG critique of the transition probabilities should not be considered as verification of the company's underlying model structure but are provided for completeness.

Transition probabilities: Netarsudil latanoprost and bimatoprost-timolol

Transition probabilities for netarsudil-latanoprost and bimatoprost-timolol were obtained directly from individual patient data (IPD) analysis of the MERCURY 3 trial. The EAG raised several clarification queries regarding the IPD data used to inform transition probabilities and the company clarified the following points:

- The transition probabilities were derived from an ITT analysis of MERCURY 3 data, based on a population of N=421 trial participants. N=9 respondents with no baseline diurnal IOP were removed pre-analysis. Transition probabilities were derived for complete cases, meaning that missing post-baseline diurnal IOPs were removed as were data points where <3 of the measurement timepoints were available. In summary, baseline data were available for 421 trial participants

(netarsudil-latanoprost: 210; bimatoprost-timolol: 211), reducing to netarsudil-latanoprost: 173; bimatoprost-timolol: 195 at the three-month time-point.

The EAG note that there are some missing data points that increase uncertainty surrounding the underlying transition probabilities up to one year for netarsudil-latanoprost and bimatoprost-timolol. However, on balance, the EAG are satisfied that the company's approach to using complete case data, based on an ITT analysis of the MERCURY 3 study population is appropriate for deriving transition probabilities.

- Data for the 'fellow' eye were not reported in the original submission with respect to transition probabilities. Following clarification, the company added additional functionality to the model to allow the use of 'fellow' eye data in the model.

  The EAG is satisfied that the base case analysis should be informed by 'study' eye data, given that the company have clarified this is most likely to be the 'worst' seeing eye. However, the EAG notes that applying the switch in the model to use the 'fellow', assumed 'best' seeing eye increases overall costs and decreases overall QALYs. This would not be the expected output of the model and further raises EAG concerns regarding the model face validity. The EAG were unable to identify any errors per se, but the model output could be a result of a lack of clarity regarding whether comparator treatments included in the NMA were for the 'best' or 'worst' seeing eye.

The underlying transition probabilities for netarsudil-latanoprost and bimatoprost-timolol remained unchanged after clarification queries.

Transition probabilities: remaining FDC comparators

The original company submission used a MAIC or STC to obtain relative treatment effects for the model. The company clarification response explains that, for the most recent model version, transition probabilities for 5 comparators are obtained from a network-meta-analysis because additional studies were available from the updated literature review post clarification that allowed a network to be constructed. It was not possible to link the final two comparators to the network based on the company's

targeted searches (brinzolamide-timolol and tafluprost-timolol). For these treatments, effectiveness was assumed to be equal to an alternative treatment from the same class. Treatment efficacy sources, by comparator class are provided in Table 15 of the company clarification response, reproduced in Table 13 below. Details of the resulting transition probabilities for each FDC comparator are reported in Tables 16-24 of the company clarification response.

Table 13 Comparator efficacy sources for all treatments included in the economic model [reproduced from Table 15 of the company's clarification response]

Comparator class	Comparator	Source of efficacy data
RKI + PGA	Netarsudil-latanoprost	MERCURY 3[6]
CAI + BB	Dorzolamide-timolol	NMA
	Brinzolamide-timolol	Assumed equal to dorzolamide-timolol
CAI + SYMP	Brinzolamide-brimonidine	NMA
SYMP + BB	Brimonidine-timolol	NMA
PGA + BB	Bimatoprost-timolol	MERCURY 3[6]
	Latanoprost-timolol	NMA
	Tafluprost-timolol	Assumed equal to bimatoprost-timolol
	Travoprost-timolol	NMA

Abbreviations: BB – Beta-blocker; CAI – Carbonic anhydrase inhibitor; NMA – Network meta-analysis; PGA – Prostaglandin analogue; RKI – Rho Kinase Inhibitor; SYMP – Sympathomimetic

The EAG would normally question the methodological appropriateness of over-riding the NMA results with the MERCURY 3 trial results for bimatoprost-timolol transition probabilities. However, given the concerns raised regarding the NMA methodology and the completeness of the network, the EAG are satisfied that it is preferable to use the MERCURY 3 data to inform transition probabilities for bimatoprost-timolol in the economic model.

The EAG note that the company have provided no evidence to support the equivalence assumptions applied for brinzolamide-timolol and tafluprost-timolol. Based on the EAG critique in Chapter 3, a full systematic review may have identified additional studies that would have allowed these treatments to be included in the network.

Transition probabilities: long-term extrapolation assumptions

Three extrapolation approaches were considered for modelling the transition probabilities between IOP percentage change health states over time. The company explored A) LOCF where the final observed cycle transition probabilities were extrapolated for the model time horizon; B) Patients remained in their cycle 3 health state without any further state transition; C) The average of all 3 cycles was applied. Option C was used for the base case analysis.

In theory, the company has provided a range of extrapolation options that would initially appear reasonable to consider in scenario analysis. The average approach used in the company's base case analysis might be reasonable because it smooths out random fluctuations in IOP over time. However, the EAG has multiple concerns with the company's approach:

- *Long term IOP transitions are highly uncertain, even whilst on treatment. With no longer-term data presented on the impact of FDC therapy on IOP, any assumptions included in the model are uncertain, and may create a bias of unknown magnitude and direction on the ICER.*

- *The company apply these transitions longer-term regardless of whether a patient is assumed to be on their initial line of FDC treatment or discontinued to a basket of other FDC comparator treatments. The company's approach does not accurately reflect the treatment pathway described in Figures 2 and 3 of this report, where patients discontinuing from FDC therapies would often require surgery or other treatments.*

- *The company's approach to modelling long term treatment effectiveness means that there are no implications on quality of life for patients who discontinue treatment due to a lack of effectiveness. For this reason, the EAG does not consider the long-term extrapolations of IOP to be plausible, even if the model structure was appropriate to capture disease progression, which it is not.*

Treatment discontinuation

Treatment discontinuation rates for netarsudil-latanoprost and bimatoprost-timolol were sourced from the MERCURY 3 trial. The original company submission assumed that treatment discontinuation rates for all remaining comparators were equal to bimatoprost-timolol. Following clarification, the company provided additional information on treatment discontinuation rates sourced from studies included in their updated, targeted clinical effectiveness literature review (Table 29). Base case persistence rates (1- treatment discontinuation) applied for each comparator are summarised in Table 31 of the clarification response document. Where two sources of data were available for a comparator, the alternative was used in scenario analysis. Assumptions of equivalence in terms of treatment discontinuation were assumed for all treatments within the same treatment class when treatment specific data were unavailable (RKI+PGA; CAI+BB; CAI+ SYMP; SYMP+BB; PGA+BB).

The inclusion of data from the updated literature review likely reduces the uncertainties and biases in the treatment discontinuation rate assumptions from the original company submission. Given the critique of the company's targeted literature review, the EAG note that the assessment of evidence is likely to remain incomplete. Whilst not complete, the EAG considers the updated treatment discontinuation sources to be acceptable and the EAG's clinical experts agree that in the absence of evidence it is reasonable to apply assumptions of equivalent treatment discontinuation rates within class of treatment.

The original company base case model assumed that treatment discontinuation rates were constant over time. The EAG initially considered this to be an over-estimate of discontinuation due to adverse events compared to what might be observed in UK clinical practice because adverse events would be most likely to cause discontinuation early during treatment. The EAG asked the company to explore the reasons for treatment discontinuation and to apply more plausible assumptions where the treatment discontinuation rate reduced over time. In response to clarification, the company provided reasons for treatment discontinuation in the MERCURY 3 trial (Table 30 of the clarification response document), noting that the majority of reasons for discontinuation were due to AEs. The company also provided additional information, where available, using IPD data (netarsudil-latanoprost and bimatoprost-timolol) to separate treatment discontinuation from the first month (likely due to

cosmetic changes) from longer term discontinuation rates, with post 1-month discontinuation rates extrapolated for the remainder of the on-treatment time horizon. For all the remaining comparators, a multiplier was applied for month 1+ vs. month 1, based on a pooled AE rate from both treatment arms in the MERCURY 3 trial.

The EAG considers it appropriate to reduce the treatment discontinuation rate over time and to use the trial ITT data where possible to inform this. However, the company's approach is highly uncertain, given the lack of available data for subsequent time periods from comparator treatments, but is plausible and based on sound logic. The EAG's clinical expert found it difficult to comment on the validity of the median time on treatment but noted that the comparators with the longest modelled time on treatment are the most widely used treatments in UK clinical practice. The EAG therefore considers the company's long-term extrapolation approach for adverse events to be reasonable, though uncertain. Treatment discontinuation curves for all treatments are reported in Figure 9 below. Whilst the EAG accepts the treatment discontinuation curves are derived from MERCURY 3 trial data for netarsudil-latanoprost and bimatoprost-timolol, the longer-term discontinuation of these treatments in UK clinical practice remains unknown. Long-term discontinuation for the remaining comparators is even less certain.

Figure 9 Company preferred treatment discontinuation curves

The company's base case economic model assumes that treatment discontinuation reduces overall modelled costs due to a reduction in treatment acquisition costs. The original submission assumed that no treatment acquisition costs were incurred following discontinuation, but this was revised in response to clarification to include a basket of alternative FDC treatments (excluding the previous treatment line). Discontinuation also impacts on adverse events by reducing adverse event management costs, for example when subsequent post-discontinuation treatments have lower AE profiles, as in the case of netarsudil-latanoprost discontinuation. Treatment discontinuation slightly increases QALYs due to a reduction in adverse events, but without any loss in effectiveness (increase in IOP) for those who discontinue from treatments with higher AE rates.

The EAG does not consider the original face validity concerns to be satisfactorily addressed post clarification. Despite some minor improvement in the face validity of modelled costs following clarification, the EAG concerns about the impact of treatment discontinuation on QALYs remains. Taking Roclanda as an example, assuming no treatment discontinuation in the model reduces the company's base case QALYs from [redacted] to [redacted]. Reductions are observed in all modelled health states because remaining on treatment increases adverse events, whilst having no impact on health state transition probabilities. Based on the company's assumption of equivalent effectiveness across all FDC comparators post discontinuation, it would usually be more cost-effective to bypass Roclanda and proceed directly to an alternative basket of FDC combination treatments in the company's current model configuration. This model output may however be valid over a short-term time-horizon, but in a treatment pathway with multiple lines of treatment, the current model structure ignores the potential for disease progression over time. Thereby, even if the current model built in multiple lines of treatments, it would still never allow reductions in QALYs due to discontinuation of any line of treatment. This lacks face validity and means the model does not adequately capture long-term cost-effectiveness of the treatment decision under consideration for this appraisal.

In addition to the face validity concerns of the company's assumptions when extrapolated over the longer term, there may also be concerns over the shorter-term appropriateness of the assumptions applied. Table 28 of the company response for clarification shows that patients who have discontinued a treatment have significantly higher IOP than those who

remain on treatment, further raising concern that the model may not adequately capture the QALY losses of increases in IOP due to discontinuing treatment.

The EAG re-iterates the primary concern with the long-term modelling that treatment discontinuation is not aligned with OHT or POAG health states, making it difficult to provide any assessment of the face validity of the treatment discontinuation curves. For example, it might be plausible that patients converting from OHT to POAG would require a change in their treatment, or patients experiencing a transition to more severe glaucoma disease. Without linking treatments to disease state, it is very difficult to provide a robust assessment of cost-effectiveness for this appraisal.

4.2.7 Health related quality of life

The company used SF36 data from the MERCURY 3 trial mapped into EQ-5D-3L, using the Ara and Brazier (2008) mapping algorithm,[48] to attach utility weights to the Markov states defined according to the IOP reduction from baseline. The EAG understands SF-36 data for baseline and 6 months for all participants were used in the mapping exercise. MERCURY 3 trial participants were classified into the three IOP reduction categories (i.e., <20%, 20 to 30%, and >30% IOP reduction) using IOP observations for baseline (screening) and 6 months (trial visit 9). The company's grouping gives higher utility weights to those with higher reductions in IOP (i.e., [redacted] and [redacted] for <20%, 20 to 30%, and >30% IOP reductions, respectively), for the company's base case.

The ERG understands the mapping algorithm used to map SF36 data to EQ-5D-3L is appropriate. However, as the SF36 instrument has been used in the MERCURY 3 trial, alternative utilities can be obtained without mapping. The EAG requested the company to provide utility scores for the Markov states defined in the company's model using the SF-6D, an alternative preference-based measure of HRQoL that can be obtained using responses to the SF-36 instrument.[49, 50] In addition, the EAG requested a scenario analysis using the SF-6D utility scores.

The company did not provide these (response to clarification question B10). The company provided mean values for a transformation of the SF-36 across a) the Physical Functioning, Role Physical, Bodily Pain, and General Health dimensions and b) Vitality, Social Functioning, Role Emotional and Mental Health. These averages give values around 3 and

cannot be interpreted as utilities and definitely are not SF-6D mean utility scores. Despite this, the data presented by the company in the response to clarification question B10, show no clear relation between IOP reduction and QoL. The company stated these results were due to small numbers and lack of a treatment effect. The EAG disagrees with this statement. The EAG understands these results are more likely due to the fact that there is no direct link between differences in IOP and QoL and that the IOP affects QoL through its effects on vision loss.

The EAG understands that the variation of IOP level is asymptomatic and is not directly associated with variations in quality of life. In the company's model, higher IOP percentage reductions are associated with higher utility weights. The EAG believes the higher utility weights associated with higher IOP reductions from the MERCURY trial, must reflect the proportion of individuals with OHT, glaucoma mild, moderate or severe that obtained IOP reductions of <20%, 20% to 30%, and >30%, and not a direct result of the IOP reduction. Moreover, the model allows for monthly bi-directional transitions between all non-Death Markov states. The EAG understand variations in IOP are asymptomatic and does not agree with the possibility of varying utility by varying IOP in the way this was modelled by the company. The EAG understands QoL reflects the severity of the underlying condition and any adverse effects of treatment and not a direct result of IOP variation.

In their initial SLR the company identified alternative HRQoL data from the LiGHT trial.[35, 51, 52] Two studies reported EQ-5D-5L utility scores by glaucoma severity: mild, moderate and severe and these were used as sensitivity analyses in response to clarification questions in an attempt to quantify the utility impact of changes in IOP due to long-term impact on glaucoma disease progression.[35, 51]

These data were not suitable to be incorporated in the model because it is not appropriate to assume that severe glaucoma equates with IOP<20% reduction, moderate equates with 20-30% IOP reduction, or that mild disease equates with >30% reduction.

In summary, the company's model assumes QALYs are accumulated through the reduction of IOP, disutilities associated with treatment adverse events and adjusted utilities by age and sex.

The company's model did not allow for utility changes due to disease progression and permitted short term increases and reductions in utility due to variations in IOP. Because of the lack utility changes due of disease progression and the short-term utility changes due to IOP variation, the ERG understands that the company's model does not properly reflect long-term effects of glaucoma and glaucoma treatment on QoL and hence the model not being fit for purpose.

4.2.8 Resources and costs

Treatment acquisition costs

The original submission from the company and the initial model calculated the treatment acquisition cost for netarsudil-latanoprost per cycle using a list price of £14.00 for a 2.5 ml bottle, equating to a cost per drop of £0.28 (based on a 0.05 ml drop conversion). However, in response to clarification queries, the company updated their conversion factor based on internal (unpublished) data, suggesting a conversion factor of 0.035 ml per drop, leading to a revised base case calculation of £0.24 per drop. A 0.05 ml drop conversion was used for all the remaining FDC comparators, based on an online conversion tool. Based on the SmPC recommended dose, the cost per drop was multiplied by the frequency per cycle (60.88 or 121.75 drops) leading to a total treatment acquisition cost per monthly model cycle. For netarsudil-latanoprost, which has 60.88 drops in the model, this cost is £14.51.

The EAG note the company's updated approach to costing in response to clarification queries. The updated costs make reference to additional data available to the company suggesting a smaller drop size for netarsudil-latanoprost of 0.035 which they suggest may further reduce the treatment acquisition costs of netarsudil-latanoprost. Given that the company have used a simple online converter to measure ml per drop conversion factor for all other treatments (0.05 ml/drop), the EAG is not satisfied that there is enough evidence to support a reduced conversion factor for netarsudil-latanoprost, but not for the other FDC comparators. The EAG view is that reducing the conversion factor for one treatment only, without a full assessment of corresponding evidence for comparators is likely to generate a bias in favour of netarsudil-latanoprost. The EAG prefers to use a consistent conversion factor for all treatments in the absence of robust evidence for the comparators because the approach is less likely to lead to biases in incremental treatment acquisition costs.

Each FDC comparator treatment acquisition cost is calculated as a weighted average cost per cycle for each FDC treatment, weighted according to market shares for branded and generic alternatives within each comparator. Unit costs are obtained from the BNF, with NHS indicative prices used for branded alternatives and drug tariff prices used for generic alternatives. The company make the point that ophthalmology is unique, in that "brand loyalty" amongst patients and prescribers means that a standardized approach of generic substitution is not appropriate. The company state that this reflects real-world practice, where doctors typically prescribe brand names due to patient preferences. They also refer to NICE guidance NG81 which they claim supports this by recommending non-generics for those unable to tolerate generic products. Taking the example of brinzolamide-timolol, the company's preferred costing approach leads to a per monthly cycle cost of £7.34, calculated as follows. Two alternatives exist on the BNF:

A) Branded timolol/brinzolamide: Azarga 10mg/5ml, with a market share of 36.26%, leading to a cost per drop of £0.11 based on a 0.05ml conversion factor and a cost per cycle of £13.45 based on an average monthly dose of 121.75 (2 drops per eye per day).
B) Generic timolol/brinzolamide10mg/5ml, with a 63.74% market share, cost per drop of £0.03, leading to a cost of £3.86 per cycle based on an average monthly dose of 121.75 (two drops per day in each eye)."

The treatment acquisition cost for brinzolamide-timolol is then calculated as ([redacted]*£13.45) + ([redacted]*£3.86) = £7.34. A similar approach is used for each comparator in the model. For all comparators, treatment administration costs are assumed to be £0 because patients typically self-administer glaucoma eye drops.

The EAG agrees that it is reasonable to assume there are no routine treatment administration costs for any of the alternatives, and this reflects the use of FDC treatments in UK clinical practice. However, the EAG raise two concerns regarding the company's approach to calculating treatment acquisition costs for FDC comparators:

1) *The EAG does not consider the company's costing approach to be appropriate. Should the committee prefer an analysis where prescriptions for glaucoma are issued in primary care, then the use of BNF costs are appropriate, but the drug tariff price should be used. The EAG does not necessarily agree that patient's commencing a new line of treatment*

will have built up brand loyalty for an FDC treatment as they have not yet experienced it. The EAG is not suggesting that patients already treated with a branded alternative should have their treatment stopped, that would be an issue for their treating clinicians to discuss with patients directly. However, for new patients, to whom NICE guidance for netarsudil-latanoprost would apply, the EAG view is that generic substitution could be considered. In the example of brinzolamide-timolol above, this would result in a reduced treatment acquisition cost of £3.86 per cycle. Applying the drug tariff price to all would lead to a cost of ([redacted]*£4.92) + ([redacted]*£3.86) = £4.24. *The EAG considers it more appropriate to cost treatments according to the drug tariff price as this more accurately reflects the costs to the NHS of prescriptions dispensed by pharmacies.*

2) *The use of BNF costs in the model implicitly assumes that the company wish to consider the use of treatments in primary care. In response to FAC, the company quote market share data further supporting this claim. The EAG's clinical expert view is that FDC comparators are usually initiated in secondary care but managed and prescribed routinely in primary care, thus supporting the use of BNF costs. However, this may differ across the country and the EAG would welcome further engagement with the clinical community on the most appropriate prescribing setting. Should it transpire that treatment is mostly prescribed in secondary care, then eMIT prices would be more appropriate.*

3) *The EAG are also concerned that there are some additional assumptions applied in the company's weighted costing approach for FDC comparators that have not been fully described or justified. For example, in the case of the generic "Dorzolamide/timolol eye drops 2% 60.2ml," the company approach to costing assumes that the cost of the branded product COSOPT "COSOPT EYEDROP U/D 60.2ML" for NHS indicative pricing at £28.59 and drug tariff pricing at £17.86. Assuming the cost of a branded treatment for the proportion of patients receiving a generic alternative based on market share data biases the company's costing in favour of netarsudil-latanoprost in the model. However, the market share for the treatment in question is comparatively small and so the magnitude of additional bias is likely to be minimal. The company provided further details outlining their assumptions at the factual accuracy check stage of the appraisal.*

Table 14 below details the company and EAG preferred costing assumptions.

Table 14 Comparison of different treatment acquisition costs for application in the economic model

Active ingredient	Product name (if not generic)	Product specific	Company Market share (%)	BNF NHS indicative price (£)	BNF Drug tariff price (£)	eMIT price (£)	Company preferred cost per cycle (£)	EAG preferred cost per cycle, primary care (£)
Brinzolamide & timolol	Azarga	Azargaeyedr5/10mg5ml	[redacted]	11.05	4.04	4.04	£7.34	£4.24
	Generic	TIMOLOL/BRINZOLAMIEYEDR5/10MG5ML	[redacted]	8.19	3.17	4.04		
Dorzolamide & timolol	Generic	Dorzolamid/timololeyedrops2%60.2ml	[redacted]	28.59	17.86	22.15	£9.56	£6.52
	Generic	DORZOL/TIMOLOLSDZEYEDROPS5ML	[redacted]	1.86	1.7	2.41		
	Generic	DORZOL/TIMOLOL ZVA EYE DROPS 5ML	[redacted]	1.86	1.7	2.41		
	Generic	DORZOLAMID/TIMOLOL EYE DROPS 5ML	[redacted]	1.86	1.7	2.08		
	COSOPT	COSOPTEYEDROPS5ML	[redacted]	10.05	1.7	2.41		
	COSOPT	COSOPTMSDEYEDROPS5ML	[redacted]	10.05	1.7	2.41		
	COSOPT	COSOPTEYEDROPU/D60.2ML	[redacted]	28.59	17.86	22.15		
	COSOPT	COSOPTIMULTIEYEDROPS10ML	[redacted]	28	28	4.82		
	EYLAMDO	EYLAMDOPFEYEDROPS5ML	[redacted]	8.13	8.13	2.41		
	VIZIDOR	VIZIDORDUOPFEYEDROPS5ML	[redacted]	8.14	8.13	2.41		
Latanoprost & timolol	Generic	Latanoprost/timoleyedrops2.5ml	[redacted]	3.52	5.2	2.03	£12.22	£7.79
	Generic	LATANOPROST/TIZVAEYEDROPS2.5ML	[redacted]	3.52	5.2	2.03		
	Generic	LATANOPRST/TIMSDZEYEDROPS2.5ML	[redacted]	3.52	5.2	1.58		
	FIXAPOST	FIXAPOSTPFE/DUDV30.2ML	[redacted]	13.49	13.49	-		
	MEDOX	MEDOX50MCG/5MG/ML2.5ML	[redacted]	14	3.47	2.03		
	XALACOM	XALACOMEYEDROPS2.5ML	[redacted]	14.32	5.2	2.03		
Tafluprost & timolol	Taptiqom	Taptiqome/d15y&5mg30.3ml	[redacted]	14.5	14.5	-	£14.71	£14.71
imatoprost &	Generic	Bimatopro/timozvaeyedrops3ml	[redacted]	14.16	14.16	7.19	£15.82	£15.32

Active ingredient	Product name (if not generic)	Product specific	Company Market share (%)	BNF NHS indicative price (£)	BNF Drug tariff price (£)	eMIT price (£)	Company preferred cost per cycle (£)	EAG preferred cost per cycle, primary care (£)
timolol	Generic	BIMATOPROST/TIMOLOEYEDROPS3ML	[redacted]	14.16	14.16	7.19		
	EYZEETAN	EYZEETANEYEDROPS3ML	[redacted]	14.16	14.16	-		
	GANFORT	GANFORTEYEDROPS33ML	[redacted]	14.16	14.16	-		
	GANFORT	GANFORTEYEDROPS3ML	[redacted]	14.16	14.16	-		
	GANFORT	GANFORTVIALSU/D30.4ML	[redacted]	17.94	17.94	-		
Travoprost & timolol	Generic	Travoprosttimololeye/dropsol2.5ml	[redacted]	6.75	4.51	-	£12.18	£5.49
	DUOTRAV	DUOTRAVEYE/DROPSOL2.5ML	[redacted]	13.95	4.51	-		
Brinzolamide & Brimonidine	SIMBRINZA	Simbrinza 10mg/ml / 2mg/ml eye drops	[redacted]	9.23	9.23	-	£11.24	£11.24
Brimonidine & timolol	Combigan	Combiganeyedrops35ml	[redacted]	27	27	-	£13.74	£16.23
	COMBIGAN	COMBIGANEYEDROPS5ML	[redacted]	10	13.22	-		

Modelled health state costs

Baseline health state resource use was informed using Gazzard et al. 2019 with multipliers reflecting increased resource utilisation in more severe cases. A 5% multiplier was applied for <20% IOP reduction, 2.5% for 20-30% IOP reduction, and 0% for >30% IOP reduction. Resource unit costs were validated by UK clinical experts and obtained from various sources (PSSRU 2022, NHS England 2021, Violato et al. 2016), then summed for each health state per cycle.

The EAG would like to re-emphasize the point that we do not consider the current model structure to accurately capture the long-term costs of glaucoma disease progression. It is not appropriate to align resource use with percentage changes in IOP whilst ignoring the underlying severity of disease. It is likely that resource use and costs would follow disease status, rather than IOP changes which are asymptomatic. A more appropriate health state model as described in Section 4.2.2 would allow for a more accurate approach to incorporating lifetime costs in the model. For that reason, the EAG does not consider the costing approach taken by the company to be appropriate for decision-making under the NICE STA framework where the reference case stipulates that all relevant costs should be included in the economic model.

Even over a short-term time horizon, which is likely to be less biased by the underlying model structure, the EAG has concerns regarding the appropriateness of the cost and resource use estimates applied to the three different IOP reduction health states. The EAG queries why the LiGHT trial was considered representative of all patients with OHT or POAG who achieve >30% reduction in IOP. The company explained that patients in the trial, on average achieved the 30% IOP reduction target. However, there would inevitably be uncertainty, and some trial participants would not have necessarily achieved the target.

Furthermore, the EAG are concerned that the multipliers applied to the remaining IOP health states are based on the opinion of one clinical expert and may not be reflective of monitoring of patients in UK clinical practice. It is unclear how the expert's views were elicited and what resources they were considering when providing multipliers. The EAG therefore notes that the true health state costs applied to different IOP percentage reductions in the model is highly uncertain.

Unit costs for resource use data were obtained from nationally representative unit cost sources, including NHS National Cost Collection 2021/22 and Unit Costs of Health and Social Care 2022.

The EAG is satisfied that the cost sources used for health state resource use and routine monitoring are appropriate. However, it was noted that, for Optometrist visits and concomitant SLT treatment, the company have inflated costs from published literature to 2022 values. Regarding SLT treatment costs, the reference (Gazzard et al. 2019)[52] indicates the total cost of a SLT is likely to be between £96 and £151 depending on the assumptions made, with the company opting to apply the upper estimate of £151 per patient for a SLT to use the more conservative estimate.[35] Similarly, for optometrist visits, the company has captured the total average cost of an optometrist-led community monitoring review at £52 per review, as reported by Violato et al., 2016.[53] Given that the resource use data from the source studies could not be easily identified, the EAG agrees that the use of inflation adjustments is likely to be an acceptable approach to obtaining health state costs.

AE costs

The economic model for the original company submission included adverse events of any severity, occurring in at least 5% of patients in either the netarsudil-latanoprost or bimatoprost-timolol arm of the MERCURY 3 trial. The company state (Section B.3.3.3 of the CS) that all grades were included in the economic model because there were no adverse events of GRADE 3 or above observed in the MERCURY 3 trial. For 3 comparators (i.e. dorzolamide-timolol; brimonidine-timolol and brinzolamide-brimonidine), it would appear that the company have reported adverse events based on a selection of studies and sources from the literature. For the remaining four comparators, studies were also sought from the literature, but where a particular AE was not reported, this was assumed equal to either bimatoprost-timolol or netarsudil-latanoprost. Table 46 of the CS shows the AE probabilities, per cycle, for all comparators included in the economic model.

In general, the EAG find the company's approach to obtaining AE rates to be confusing and lacking transparency. Assumptions are not clearly described, and it is difficult to re-produce the exact assumptions used in the economic model due to hard coding or AE rates. For example, it would appear that probabilities marked as academic in confidence in the

submission apply assumptions of equality to either netarsudil-latanoprost or bimatoprost-timolol, but the justification for these assumptions is unclear.

Furthermore, the company do not appear to have updated their AE rates for comparators using the additional literature obtained as part of the updated clinical effectiveness review for the NMA. The company has not provided a strong justification for the selective use of AE rate evidence in the model. Whilst the EAG would have preferred the use of AE data sourced directly from the included studies in the updated NMA, the EAG's clinical expert is of the view that the assumptions of equivalence, if denoted by AIC marking, appear to be broadly reasonable. However, if the assumptions of equivalence are triggered due to missing data in source studies, then there is a risk that missing data simply reflect that there were no such AEs observed in the comparator treatments. This would likely provide a bias in favour of both netarsudil-latanoprost and bimatoprost-timolol.

The use of additional literature from the identified studies may have provided useful information to populate the economic model and may have negated the need for multiple assumptions of AE rate equivalence to different arms of the MERCURY 3 trial.

The per-cycle probability of adverse events was multiplied by a unit-cost for each adverse event. Many AEs were assumed to include visits to ophthalmology, eye-drops, or GP visits, in addition to the resource use incurred for routine monitoring. Details of resource use assumptions and unit costs applied to each adverse event are summarised in Table 58 of the company submission.

The EAG is concerned that the approach to ascertaining resource use assumptions for each adverse event in the economic model is not clearly described. Resource use (e.g., frequency of ophthalmology appointments to manage AEs) is obtained from company sought UK clinical expert opinion, but it is unclear how many experts were consulted or how representative their views are of UK clinical practice. Considering that none of the AEs were Grade III or above, the EAG's view is that the AE costs in the model are an over-estimate of the costs that would be incurred in UK clinical practice. Patients are often reminded that some redness (conjunctival hyperemia) can be expected, and many experiencing such events would wait until their routine appointments to discuss minor events with their clinical team. The EAG are concerned that there is a risk of double counting adverse event and routine monitoring costs in the model. The EAG's clinical expert has therefore reviewed the costs applied to each adverse event in the model and provided an alternative set of assumptions

regarding resource use for each AE. These assumptions are based on an adverse event assumed to be of moderate severity (Grade II on average). The proportion receiving resource is intended to reflect the proportion of patients experiencing each event that would require an additional ophthalmology consultation outside of the normal scheduled routine monitoring. The EAG would welcome additional consultation on the management of adverse events for OHT and POAG patients, to ensure that our assumptions are generalisable more broadly across the UK. The company and EAG preferred assumptions are compared in Table 15 below. A further scenario analysis, removing additional costs of adverse events is also provided to illustrate the magnitude of impact on the ICER.

Table 15 Comparison of EAG and company preferred AE resource use assumptions

Adverse event	AE resource use	Company preferred assumptions			EAG preferred assumptions			
		Proportion requiring resource	N visits per AE:	Total AE cost (£)	Relevant to include (Y/N)	Proportion requiring resource	N visits per AE	Total AE cost (£)
Conjunctival hyperaemia	Ophthalmology appointments	100%	1.5	212.96	Y	30%	0	0.00
Cornea verticillata	Ophthalmology appointment	100%	1.0	141.97	Y	50%	0	0.00
Conjunctival haemorrhage	Ophthalmology appointment	100%	2.0	283.95	Y	50%	1	70.99
Eye pruritis	Ophthalmology appointment	100%	1.5	441.41	Y	50%	1	70.99
	Dermatology appointment	100%	1.5		Y	10%	0	
Punctate keratitis	Ophthalmology appointment	100%	2.5	354.93	Y	50%	1	70.99
Conjunctivitis allergic	Ophthalmology appointment	100%	2.0	283.95	Y	100%	1	141.97
Viral URTI	GP appointment	100%	1.0	42.00	N	N/A	N/A	0.00
Hypertension	NHS England, 2021 listed cost	100%	--	537.86	N	N/A	N/A	0.00
Abnormal vision	Ophthalmology appointment	100%	2.0	283.95	Y	100%	1	141.97
Blurred vision	Ophthalmology appointment	100%	2.0	283.95	Y	100%	1	141.97

Adverse event	AE resource use	Company preferred assumptions			EAG preferred assumptions			
		Proportion requiring resource	N visits per AE:	Total AE cost (£)	Relevant to include (Y/N)	Proportion requiring resource	N visits per AE	Total AE cost (£)
Change of eyelashes	No treatment required	--	--	0.00	Y	N/A	N/A	0.00
Conjunctival blanching	No treatment required	--	--	0.00	Y	N/A	N/A	0.00
Dry eye	Hypromellose eye drops x1 (1-2 drops three times per day as needed)	100%	--	0.69	Y	100%	N/A	0.00
Eye allergy	Ophthalmology appointment	100%	2.0	283.95	Y	100%	1	141.97
Eye irritation	Hypromellose eye drops x1 (1-2 drops three times per day as needed)	100%	--	0.69	Y	100%	N/A	0.00
Eye pain	Ophthalmology appointment x2	100%	2.0	283.95	Y	100%	1	141.97
Eyelash discolouration	No treatment required	--	--	0.00	Y	--	--	0.00
Foreign body sensation in eyes	Ophthalmology appointment	100%	2.0	283.95	Y	100%	1	141.97
Headache	Paracetamol x1 (1-2 tablets up to four times a day)	100%	--	2.44	N	100%	--	0.00
Ocular discomfort	Ophthalmology appointment	100%	2.0	283.95	Y	50%	1	70.99

Adverse event	AE resource use	Company preferred assumptions			EAG preferred assumptions			
		Proportion requiring resource	N visits per AE:	Total AE cost (£)	Relevant to include (Y/N)	Proportion requiring resource	N visits per AE	Total AE cost (£)
Ocular hyperaemia	No treatment required	--	--	0.00	Y	--	--	0.00
Photophobia	Ophthalmology appointment	100%	2.0	283.95	Y	50%	1	70.99
Visual disturbance	Ophthalmology appointment	100%	2.0	283.95	Y	50%	1	70.99

Post treatment discontinuation costs.

The EAG were concerned that the original company submission did not incorporate any post treatment discontinuation treatment costs, which was not appropriate and lacked face validity. In response to clarification, the company provided an updated set of analyses. The updated model assumes that the proportion of the cohort who discontinue treatment in any given cycle of the model would incur the costs of a second line basket of FDC therapies. The costs of this basket were calculated using a weighted average of the comparator treatments used at first line (with the removal of the product they were discontinuing from). The weighting was based on the company's available 5-year market share data and included treatment acquisition and administration costs, with adjustment for compliance where required. The basket included a mix of branded and generic products, and the revised base case assumed this would be incurred up to the median model time horizon, after which the cohort would switch to generics. The time at which generic substitution was assumed was tested in scenario analyses.

The EAG accept that the company's revision makes minor improvements in the face validity concerns raised at clarification queries. However, the appropriateness of the assumptions applied are questionable. For example, the company's approach does not include an option for treatment escalation in patients who discontinue treatment due to a lack of effectiveness and / or disease progression. They also do not address the need for the model to incorporate surgery linked to disease progression and / or failure on multiple lines of treatment. In summary, the EAG appreciate that the company's assumptions to discontinue patients to a basked of alternatives might be appropriate in the short term (e.g. over 1 year), but is not appropriate for a model with a lifetime horizon. The company's revised approach and scenario analyses are described in Table 16 below. The EAGs approach, as with first line treatments is to use drug tariff prices, with prescription in primary care, where possible.

Table 16 Variation in the weighted cost following discontinuation (reproduced from Table 27 of the company's clarification response)

Intervention	Average cost per cycle, post discontinuation		
	Base case	No shift to generics	Immediate shift to generics
Netarsudil-latanoprost	£14.77	£12.89	£14.51
Brinzolamide & Timolol	£14.81	£13.68	£14.51
Dorzolamide & Timolol	£14.85	£13.81	£14.51
Latanoprost & Timolol	£15.25	£13.03	£15.28
Tafluprost & Timolol	£14.76	£12.94	£14.51
Bimatoprost & Timolol	£8.30	£10.50	£6.30
Travoprost & Timolol	£14.77	£12.99	£14.55
Brinzolamide & brimonidine	£14.79	£13.17	£14.51
Timolol & Brimonidine	£14.75	£12.99	£14.51

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

Original company submission

The company's original base case cost-effectiveness results for pairwise comparisons versus netarsudil-latanoprost and fully incremental analyses, are reported in Tables 17 and 18 respectively for information. In the original submission, netarsudil-latanoprost was the least effective of all treatments in terms of QALYs accrued over the lifetime model time horizon (due to marginally lower point estimates of effectiveness – IOP reduction). Netarsudil-latanoprost had lower costs compared to all FDCs (except brinzolamide-timolol), placing NL in the SW quadrant of the cost-effectiveness plane for all but one of the pairwise comparisons. Considering a threshold value of a QALY of £20,000, NL was cost-effective, in the SW quadrant of the CE plane compared to Trav-Tim, Lat-Tim, Taf-Tim, Bim-Tim and Brim-Tim, with ICERs over £20,000. However, for the fully incremental analysis, all but one treatment strategy was dominated by Brin-Tim and this was the optimal treatment strategy overall.

Whilst the ICERs presented are technically accurate, the EAG note that for decision making, the committee may want to consider ICERs for netarsudil-latanoprost vs. each comparator, as opposed to for each comparator versus netarsudil-latanoprost as reported in the original company submission. The EAG has therefore inverted the comparison from the original submission and post-clarification analyses to ensure that all results are reported consistently throughout the report.

[redacted]Table 17 Original base-case results (pairwise comparison versus netarsudil-latanoprost), [reproduced from Table 63 of the company's submission]

Technologies	Total costs (£)	Total QALYs	Incr. Costs (£) NL vs. comp[A]	Incr. QALYs NL vs. comp[A]	ICER (£) NL vs. comp[A]
Netarsudil-latanoprost	[redacted]	[redacted]	-	-	-
Brinzolamide-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Travoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	1,778,704 (SW)
Dorzolamide-timolol	[redacted]	[redacted]	[redacted]	[redacted]	688 (SW)
Latanoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	578,782 (SW)
Tafluprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	66,858 (SW)
Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	60,284 (SW)
Brimonidine-timolol	[redacted]	[redacted]	[redacted]	[redacted]	172,645 (SW)
Brinzolamide-brimonidine	[redacted]	[redacted]	[redacted]	[redacted]	4,079 (SW)

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years; SW = South-west quadrant of the cost-effectiveness plane

[A] Incremental costs, QALYs and ICER are adapted by the EAG to present a comparison for netarsudil-latanoprost vs. each FDC comparator to maintain consistency with the remainder of the report.

Table 18 Original fully incremental base-case results (treatments ranked in ascending order of costs) [reproduced from Table 64 of the company's submission]

Technologies	Total costs (£)	Total QALYs	Incr. Costs (£)	Incr. QALYs	Fully incremental analysis ICER (£)
Brinzolamide-timolol	[redacted]	[redacted]	-	-	-
Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Dorzolamide-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Brinzolamide-brimonidine	[redacted]	[redacted]	[redacted]	[redacted]	342,699
Brimonidine-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Latanoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Travoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Tafluprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Company updated results post-clarification.

The company's updated base case results in response to clarification queries are provided in Tables 19 and 20 below for the pairwise and fully incremental comparisons respectively. The company have added details of incremental NMB (compared to netarsudil-latanoprost for the pairwise comparison table and compared to the lowest cost treatment for the fully incremental analysis) to improve interpretation of results.

In the revised submission post clarification queries, netarsudil-latanoprost was the third least effective of all treatments in terms of QALYs accrued, only achieving QALY gains compared to Trav-Tim and Lat-Tim. Netarsudil-latanoprost had higher costs compared to all FDCs, except Trav-Tim, Lat-Tim and Taf-Tim. Net-Lat was dominated by 5 comparators, dominated 2 comparators, and had an ICER <£20,000 (unlikely to be cost-effective) compared to one other comparator in the SW quadrant. From the pairwise comparisons, NL only had a higher NB when compared to Trav-Tim and Lat-Tim. For the fully incremental analysis, Bim-Tim was the least costly treatment overall and was also the optimal treatment strategy overall.

The EAG are concerned that the labelling and presentation of the company's results lack transparency and are difficult to interpret. This is due to labelling of table names and headings for the base case results that do not accurately describe the data presented, may be misleading and are inconsistent with the presentation of scenario analysis results. The EAG has attempted to revise these to allow a more transparent interpretation of the results by making the following amendments to the presentation of Table 89 (pairwise comparisons) from the company clarification response document.

- *Treatment strategies for the pairwise comparison in Table 89 of the company clarification response were re-ordered to align with company's ordering of treatment strategies for presentation of scenario analysis results. The purpose of this amendment was to make it easier to compare the results of scenario analyses for the pairwise comparisons.*
- *Company presentation was confusing, with incremental costs and incremental QALYs reported for Comparator vs. NL, but ICERs and INB reported for NL vs. Comp. Labelling has been amended to improve consistency between table names and column headings. The results have been updated to present incremental costs, incremental QALYs, ICERs and INB for netarsudil latanoprost vs. each comparator (including ICERs and INB)*

For the fully incremental analysis (Table 90 of the company clarification response), the EAG had similar concerns around labelling and transparency of result reporting. Table 19 below makes the following adaptions to the company's presentation of results:

- *It would appear as if the company's ranking of treatment strategies (in ascending order of costs) was inaccurate, but this did not appear to impact on the accuracy of the reported results. Nonetheless, the EAG has presented the correct ranking below.*
- *It is not clear what the heading "NMB" refers to in the fully incremental analysis table, or what calculation is being performed. Upon further investigation, the company appear to have calculated incremental net monetary benefit, for the lowest cost treatment strategy compared to each of the remaining treatment alternatives. The EAG has updated the table labelling accordingly to make this more transparent.*
- *The EAG consider the presentation of INB from 2 above to be misleading and not what was intended in the clarification letter. The EAG does not consider it particularly useful to assess the INB for the lowest cost treatment alternative compared to each comparator because readers may mis-interpret the results. To aide comparison across different scenarios, it is more useful to consider NMB for each treatment strategy to enable a ranking of treatments and an assessment of the optimal treatment strategy based on maximum NMB across all comparators. An additional column with calculated NMB has been added to the table based on an assumed WTP threshold value of £30,000 per QALY.*

At the factual accuracy check stage of the process, the company identified a minor error in their economic model with respect to costing for brimonidine-timolol. This only had a minor impact on the ICERs. However, the EAG has updated the company's submitted cost-effectiveness analyses in the tables that follow, to correct this error.

Table 19 Post-clarification base-case results (netarsudil-latanoprost vs. comparators) [adapted from Table 89 of the company's clarification response]

Technology	Total Cost	Total QALY	Incremental Cost (NL vs comparator)	Incremental QALY (NL vs. comparator)	ICER (NL vs. Comparator)	INMB (NL vs. Comparator)

Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
Brinzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Dorzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Latanoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	[redacted]
Tafluprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	18759	[redacted]
Bimatoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Brimonidine and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Travoprost and Timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominating	[redacted]
Brinzolamide and brimonidine	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NL – Netarsudil-latanoprost; INMB – Incremental net monetary benefit; QALYs – Quality-adjusted life years

[redacted]Table 20 Post-clarification base case fully incremental results (treatments ranked in ascending order of costs) [adapted from Table 90 of the company's clarification response]

Technologies	Total costs (£)	Total QALYs	Incr. Costs (£)[A]	Incr. QALYs[A]	ICER (£)[A]	Incremental NMB [C]	EAG calculated NMB

Bimatoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	£191,018
Brinzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]	£190,826
Brinzolamide and brimonidine[B]	[redacted]	[redacted]	[redacted]	[redacted]	41,529	[redacted]	£190,874
Dorzolamide and timolol[B]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]	£190,694
Brimonidine and timolol	[redacted]	[redacted]	[redacted]	[redacted]	49,797	[redacted]	£190,846
Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]	£190,305
Latanoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]	£190,052
Tafluprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]	£190,306
Travoprost and Timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]	£189,323

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

[A] vs. next least costly, non-dominated option. For example, the ICER for Brin-brim reports a comparison of Brin-brim vs. Bim-tim.

[B] Rankings were incorrectly reported in the company clarification response.

[C] Company have reported INB for the cheapest treatment alternative vs. each of the remaining comparators.

5.2 Company's sensitivity analyses

Company updated results post-clarification (one-way sensitivity analyses)

The company have reported the results of a series of one-way sensitivity analyses. Ten model parameter inputs were varied between the lower and upper bounds of their confidence intervals. Tabulated results showing NMB at the lower and upper bounds are reported in Tables 124-131 of the company clarification response for netarsudil-latanoprost vs. each FDC comparator. Corresponding tornado diagrams are illustrated in Figure 20-27 of the company clarification response. The key findings are as follows.

- For the comparisons against brinzolamide-timolol, dorzolamide-timolol, latanoprost-timolol, and brinzolamide-brimonidine comparison, the NMB was, in general, most sensitive to the second-line cost per cycle following treatment discontinuation.

    - For the tafluprost-timolol and bimatoprost-timolol comparisons, the NMB was most sensitive to the second line cost of netarsudil-latanoprost per cycle, the utility for the >30% reduction in IOP health state and the first line treatment acquisition cost per cycle for both treatments respectively.

    - For the travoprost-timolol comparison, the NMB was most sensitive to the utility values related to the >30% reduction in IOP and 20-30% reduction in IOP health states, as well as the second-line cost per cycle of netarsudil-latanoprost.

    - For the brimonidine-timolol comparison, the NMB was most sensitive to the utilities for the >30% reduction in IOP and 20-30% reduction in IOP health states and the second line cost per cycle of brimonidine-timolol and netarsudil-latanoprost.

The EAG is satisfied that the company have explored the most important drivers of NMB in their one-way sensitivity analyses. However, caution is required when interpreting these, and all results from the model and they should be considered in light of the substantial EAG concerns raised throughout Chapter 4, primarily relating to the inappropriate model structure to capture lifetime costs and QALYs, and the lack of face validity of QALY results

following treatment discontinuation. For these reasons, looking at the impact of individual parameters on results may be misleading with regards to cost-effectiveness.

Company updated results post-clarification (Scenario analyses)

The company provided a range of scenario analyses in response to clarification queries and updated their original scenario analyses applied to their new base case. The full range of scenario analysis output is reported in Tables 132 to 147 of the company's clarification response document. Both deterministic and probabilistic ICERs are reported.

The EAG is satisfied that the scenario analyses are implemented as described in the company's documentation. The EAG considers it more helpful to consider the scenario analyses results in terms of NMB, which makes it easier to identify parameters which are most likely to impact on the decision problem. Table 21 below summarises the NMB for each treatment strategy and Table 22 provides the corresponding NMB rankings, with 1 being the optimal treatment strategy (highest NMB) and 9 being the least cost-effective (lowest NMB). Grey shaded cells draw attention to the NMB for bim-tim and net-lat because this comparison is based on data from the MERCURY 3 trial and could be considered more robust than comparisons to the other FDCs, if the EAGs concerns outlined in Chapter 4 were addressed. The results show that across all scenario analyses conducted by the company, bim-tim is consistently one of the highest ranked treatment options, whilst net-lat is consistently one of the lowest ranked treatment options. The company's base case and scenario analyses show that netarsudil-latanoprost is unlikely to be considered the optimal treatment option.

Table 21 EAG summary of company's scenario analyses, NMB results reported by treatment strategy.

Scenario	Net-Lat	Brin-Tim	Dor-Tim	Lat-Tim	Taf-Tim	Bim-Tim	Brim-Tim	Trav-Tim	Brin-Brim
Base Case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BNF cost type - tariff	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BNF cost type - NHS indicative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Compliance rate 90%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Compliance rate 80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transition matrices - LOCF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transition matrices - final	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative persistence references	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude age adjusted utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount 1.5% cost and outcomes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount 1.5% costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount 1.5% outcomes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon - 5years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon - 15years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transition probabilities - fellow-eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE probabilities x2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE probabilities x3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS utility - Stein	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS utility - Orme	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude wastage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Net-Lat	Brin-Tim	Dor-Tim	Lat-Tim	Taf-Tim	Bim-Tim	Brim-Tim	Trav-Tim	Brin-Brim
HS resource multiplier - 3.5% & 5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS resource multiplier - 5% & 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS resource multiplier - 10% & 15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NMA Fixed effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QoL Rowen mapping	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 22 EAG summary of company's scenario analyses, NMB ranking by treatment strategy

Scenario	Net-Lat	Brin-Tim	Dor-Tim	Lat-Tim	Taf-Tim	Bim-Tim	Brim-Tim	Trav-Tim	Brin-Brim
Base Case	7	3	5	8	6	1	2	9	4
BNF cost type - tariff	8	2	5	7	6	1	3	9	4
BNF cost type - NHS indicative	7	4	5	8	6	1	2	9	3
Compliance rate 90%	7	3	5	8	6	1	2	9	4
Compliance rate 80%	7	4	5	8	6	1	2	9	3
Transition matrices - LOCF	7	3	5	8	6	2	1	9	4
Transition matrices - final	7	3	5	8	6	2	1	9	4
Alternative persistence references	7	3	5	8	6	1	2	9	4
Exclude age adjusted utility	7	3	5	8	6	1	2	9	4
Discount 1.5% cost and outcomes	7	3	5	8	6	1	2	9	4
Discount 1.5% costs	7	3	5	8	6	1	2	9	4
Discount 1.5% outcomes	7	3	5	8	6	1	2	9	4
Time horizon - 5years	7	1	4	8	6	5	3	9	2
Time horizon - 15years	7	3	5	8	6	2	1	9	4
Transition probabilities - fellow-eye	7	4	5	8	6	1	2	9	3
AE probabilities x2	7	3	5	8	6	2	1	9	4
AE probabilities x3	7	3	5	8	6	4	1	9	2
HS utility - Stein	7	5	6	8	4	2	1	9	3
HS utility - Orme	8	5	6	7	3	2	1	9	4
Exclude wastage	7	3	5	8	6	1	2	9	4

Scenario	Net-Lat	Brin-Tim	Dor-Tim	Lat-Tim	Taf-Tim	Bim-Tim	Brim-Tim	Trav-Tim	Brin-Brim
HS resource multiplier - 3.5% & 5%	6	2	4	9	8	1	5	7	3
HS resource multiplier - 5% & 10%	6	2	4	9	8	1	5	7	3
HS resource multiplier - 10% & 15%	6	2	4	9	8	1	5	7	3
NMA Fixed effect	7	4	5	8	6	1	2	9	3
QoL Rowen mapping	7	2	5	8	6	1	4	9	3

Company updated results post-clarification (probabilistic sensitivity analyses)

The mean probabilistic results broadly align with the deterministic findings. Each pairwise comparison is plotted on the incremental cost-effectiveness plane (ICEP) for netarsudil-latanoprost vs each FDC comparator in Figure 18 of the company response to clarification queries. The results show that netarsudil-latanoprost is generally more costly but less effective than most FDC comparators, with mean PSA points displayed in the north-west quadrant. The fully incremental results are reported in Table 123 of the clarification response (re-produced in Table 23 below). Probabilistic ICERs are reported alongside deterministic ICERs for each of the company's scenario analyses.

The key probabilistic results remain similar to the deterministic analyses. Netarsudil-latanoprost is dominated by 5 comparators, dominant over 2 comparators and is less costly and less effective than tafluprost-timolol. At a threshold value of £20,000 per QALY, bimatoprost-timolol is the most likely strategy to be cost-effective ([redacted] probability of being the optimal strategy), followed by brimonidine-timolol ([redacted] probability of being the optimal strategy). Netarsudil-latanoprost has only a [redacted] probability of being the optimal treatment strategy at a WTP threshold of £20,000 per QALY and is one of the least likely treatments to be cost-effective under the company's base case assumptions.

Table 23 Post-clarification base case fully incremental probabilistic results (treatments ranked in ascending order of costs) [reproduced from Table 123 of the company's clarification response]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Bimatoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	-
Brinzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Dorzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Brinzolamide and brimonidine	[redacted]	[redacted]	[redacted]	[redacted]	44,903
Brimonidine and timolol	[redacted]	[redacted]	[redacted]	[redacted]	57,488
Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Latanoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Tafluprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Travoprost and Timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Figure 10 Cost-effectiveness acceptability curve for company base case analysis [reproduced from Figure 19 of the company's clarification response]

5.3 Model validation and face validity check

The company submission stated that the economic model has undergone internal and external validation by experts. Prior to the development of the cost-effectiveness model, a protocol was developed to outline the key modelling assumptions and inputs to be implemented. This protocol was shared with a UK clinical expert to confirm the appropriateness and suitability of the model structure and health states.

The EAG raise several concerns with the appropriateness of the clinical validation of the economic model structure, and in particular, the plausibility of its long-term cost and QALY outputs. These concerns are outlined in detail throughout Chapter 4. The company's documentation is unclear as to how the clinical expert was identified by the company, whether they had any knowledge of economic modelling or experience of expert elicitation for modelling. Additionally, the EAG would recommend clinical validation from a range of experts, perhaps through an advisory board meeting, rather than relying solely on one expert's opinion.

The EAG's clinical experts agree that the aim of treating glaucoma and OHT is to reduce IOP. This is aligned with the company's sought expert opinion. However, the reason for seeking reductions in IOP is to prevent conversion from OHT to glaucoma, and to slow progression of glaucoma amongst those that have it. The EAG's clinical experts are therefore of the view that whilst changes in IOP are clinically meaningful and necessary to achieve clinical success, they alone are insufficient to capture longer-term impacts of glaucoma on costs and quality of life. The EAG view is that an appropriately valid model to capture lifetime costs and outcomes should use a linked evidence approach to map changes in IOP to the risk of developing and progressing through more severe glaucoma health states. The idea is much like managing markers of cardiovascular disease such as cholesterol and blood pressure, the goal of which is to reduce cardiovascular events and their associated costs and impacts on quality of life in the future.

Despite the concerns with the overall modelling structure, the EAG has proceeded to quality check the model functionality and parameterisation using the black-box checklist described by Tappenden and Chilcott 2014.[54] Checks were conducted for face validity of model outputs, and a closer inspection of formulate for a random selection of calculation cells and on the model trace. The findings of the EAG checks are provided in Table 24.

Table 24 Selected 'Black box' verification checks conducted on the company's base case model.

Model component	Model test	Unequivocal criterion for verification	Issues identified / ERG comment
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks, or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	All treatments produce equal estimates of total LYGs after setting the relative treatment effect in NMA.
	Sum expected health state populations at any model time-point (state transition models)	Total probability equals 1.0	No issues identified.
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	A QALY equals zero, and LYGs produce equal estimates.
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	No issues identified.

Model component	Model test	Unequivocal criterion for verification	Issues identified / ERG comment
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	No issues identified.
Cost estimation	Set intervention costs to 0	ICER is reduced*	No issues identified.
	Increase intervention cost	ICER is increased*	No issues identified.
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	No issues identified.
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	No issues identified.
General	Set all treatment-specific parameters equal for all treatment groups	Costs and QALYs equal for all treatments	No issues identified.
	Amend value of each individual model	ICER is changed	No issues identified.

Model component	Model test	Unequivocal criterion for verification	Issues identified / ERG comment
	parameter*		
	Switch all treatment-specific parameter values*	QALYs and costs for each option should be switched	Not feasible to complete due to vast numbers of comparators and parameters across multiple model sheets. Selected random checks did not identify any errors.
ICER incremental cost-effectiveness ratio, LYG life-years gained, QALY quality-adjusted life-year * Note this assumes that the parameter is part of the total cost function and/or total QALY function			

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG has raised several major critique points in Chapter 4 that have a direct impact on the validity of cost-effectiveness results when estimating lifetime horizon costs and QALYs. The main concern is that the model structure does not accurately capture glaucoma disease progression over time, and hence the long-term benefits and costs of reductions in IOP cannot be estimated with the company's model. The expected value cost and QALY outputs from the model, used to determine lifetime horizon cost-effectiveness are therefore unsuitable for decision making. Given the time constraints for an EAG report within the STA process (5-6 weeks from company's clarification response), and the lack of direct access to all the company's IPD data, it has been impossible for the EAG to build the ideal model structure for this appraisal, though we provide some guidance in Chapter 4 for the company, should they wish to do this.

Given the significant concerns with the face validity of model outputs, driven by the inappropriate model structure, the EAG has chosen not to report any exploratory analyses using the company's economic model over a lifetime horizon. The EAG strongly believe that to do so would be misleading and for a lifetime assessment of costs and QALYs associated with changes in IOP, a full glaucoma health state transition model is required.

The EAG has also raised significant concerns regarding the conduct of the NMA, which shows treatment effect sizes for change in IOP from baseline that are centred around 0. However, credible intervals from the company's NMA are extremely wide, and the EAG is unable to rule out the potential for clinically meaningful differences between groups. For the comparison of netarsudil-latanoprost vs. bimatoprost-timolol, the MERCURY 3 study shows that, at 3 months follow-up, there are no differences in IOP at 2 out of 3 measurement timepoints. For AM measurements, netarsudil-latanoprost had significantly higher IOP, but these differences were unlikely to be clinically meaningful. Given the evidence from the MERCURY 3 study, the committee may wish to consider the findings from the model over a shorter

time horizon, e.g., 1 year, where the limitations of the model structure have less impact on the validity of the cost-effectiveness findings. The EAG therefore provides several scenario analyses comparing treatment acquisition costs, adverse event costs and adverse event disutilities for each of the treatment options, based on assumption of equal efficacy between netarsudil-latanoprost and bimatoprost-timolol. Given the uncertainty of the evidence base from the NMA, we do not consider it appropriate to consider equal effectiveness for other treatment options.

The results of EAG analyses, reporting simplified analyses over a one-year time horizon are detailed in Table 25 below.

Table 25 EAG exploratory analyses applied to the company's base case analysis (deterministic)

	Scenario	Total costs	QALYs	Incremental costs [A]	Incremental QALYs [A]	ICER [A]
1	**Company's base case (lifetime horizon, company preferred model structure)**					
	Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
2	**One year time horizon to minimize impact of model structural issues on results**					
	Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
3	**Apply equivalent ml/drop conversion factors to all treatments**					
	Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
4	**Apply drug tariff prices (assumes primary care prescribing)**					
	Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
5	**Apply EAG preferred adverse event resource use**					
	Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	

	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
6	**EAG's preferred assumptions, costs over a one year (Scenarios 2-5 combined)**					
	Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
7	**6 + Assume equal effectiveness**					
	Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	N/A
8	**6 + 7 + one full year on treatment (no treatment discontinuation)**					
	Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	N/A

Abbreviations: EAG: external assessment group; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

[A] Incremental analyses reported for netarsudil latanoprost vs. bimatoprost timolol. [B] Scenario analyses applied as univariate changes.

6.2 EAG's preferred assumptions

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The company's preferred approach was to include only selected monotherapies in the network meta-analysis. The EAG prefers either to include all monotherapies from a systematic review or to pursue a more robust systematic approach to ensure effect estimates are not sensitive to the included trials or comparators. For example, they could have focused on a subset of monotherapy trials based on pre-specified criteria.

- The company prefers an economic model structure that captures intermediate, short-term changes in IOP, whereas the EAG is of the opinion that a model structure that uses a linked evidence approach to map changes in IOP to risk of conversion from OHT to glaucoma and risk of glaucoma disease progression. The EAG's preferred model structure would more appropriately capture the long-term implications of changes in IOP on costs and quality of life.

- The company preferred approach assumes comparator costs, based on average market shares of branded (costed using NHS indicative prices) and generic (costed using drug tariff prices) alternatives. The EAG prefers to use drug tariff prices as these reflect the costs paid to pharmacies for prescribing in primary care.

- The company prefers to include more intensive management costs for adverse events, including multiple secondary care contacts for all patients experiencing events regardless of severity. The EAG's preferred adverse event costs are based on the EAG's clinical expert opinion and apply lower adverse event management costs.

6.3 Conclusions of the cost effectiveness section

Overall, the EAG considers the company's NMA results to be highly uncertain. There is insufficient evidence to determine whether all treatments can be considered as providing similar clinical outcomes, and the NMA results do not rule out clinically meaningful differences. The EAG does not consider the company's economic model

structure to meet the requirements of the NICE reference case, in that it does not capture all the relevant long-term costs and health consequences of changes in IOP. The EAG's preferred approach would be to build an economic model structure that captures all relevant long-term costs and QALYs. This could be achieved by using a linked evidence approach to model the impact of changes in IOP on the risk of conversion from OHT to glaucoma and the risk of glaucoma disease progression. The company could have drawn on several examples from the published literature where this is achieved.

The EAGs concerns regarding the economic model structure may be less problematic if the committee wished to assess the evidence over a shorter time horizon, focusing on a comparison of costs only. Such an analysis could be presented over a one-year time horizon for example. The EAG has provided several scenario analyses that present a simplified costing and cost-effectiveness assessment over a one-year time horizon. It should be noted that these analyses require strong assumptions of treatment efficacy equivalence, which have not been adequately demonstrated by the company's NMA. Assessments of equivalence compared to bimatoprost-timolol may be more appropriate, and the EAG's clinical experts are confident that the MERCURY 3 trial results rule out any clinically meaningful differences in IOP change between trial arms.

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50. Rowen D, Brazier J, Roberts J. Mapping SF-36 onto the EQ-5D index: how reliable is the relationship? Health Qual Life Outcomes. 2009;**7**:27.

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52. Gazzard G, Konstantakopoulou E, Garway-Heath D, et al. Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial: Six-Year Results of Primary Selective Laser Trabeculoplasty versus Eye Drops for the Treatment of Glaucoma and Ocular Hypertension. Ophthalmology. 2023;**130**(2):139-51.

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Single Technology Appraisal

Netarsudil-latanoprost for previously treated open-angle glaucoma or ocular hypertension [ID1363]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 28 November** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 47: "Of those 8 studies, seven use model health starts and structures that attempt to capture conversion from OHT to glaucoma and / or glaucoma disease progression (one study could not be assessed as it was only available as a conference abstract)."	The company propose the wording on page 47 is edited to read: "Of those eight studies, seven use model health states and structures that attempt to capture conversion from OHT to glaucoma and / or glaucoma disease progression (one study could not be assessed as it was only available as a conference abstract)."	Typographical error.	Thank you, report amended as suggested.
On page 53: "The ERG understands that, in a glaucoma model, long term health related quality of life should be primarily associated to the vision loss and severity of glaucoma."	The company propose the wording on page 53 is edited to red: "The ERG understands that, in a glaucoma model, long term health related quality of life should be primarily associated with the vision loss and severity of glaucoma."	Unclear wording.	Thank you, report amended as suggested.
On page 57: "However, the company's current model structure captures the lifetime impact of glaucoma on costs and	The company propose the wording on page 57 is edited to read: "However, the company's current model structure does not capture the lifetime impact of glaucoma on costs and outcomes (See Section 4.2.2)."	Missing word.	Thank you, report amended as suggested.

outcomes (See Section 4.2.2)."			
On page 62: "The inclusion of data from the updated literature review likely reduces the uncertainties and biases in the treatment discontinuation rate assumptions from the original company submission."	The company propose the wording on page 62 is edited to read: "The inclusion of data from the updated literature review reduces the uncertainties and biases in the treatment discontinuation rate assumptions from the original company submission."	Inaccurate wording.	Not a factual inaccuracy, no change made.
On page 69: "Two alternatives exist on the BNF: A) Branded Azarge 5lm, with a market share of [redacted]%, leading to a cost per drop of £0.11 based on a 0.05ml conversion factor and a cost per cycle of £13.45 based on an average monthly dose of 121.75 (two drops per day in each eye). B) Azarga 5ml PI, with a [redacted] market share, cost per drop of £0.03, leading to a cost of £3.86 per cycle."	The company propose the wording on page 62 is edited to read: "Two alternatives exist on the BNF: A) Branded timolol/brinzolamide: Azarga 10mg/5ml, with a market share of [redacted]%, leading to a cost per drop of £0.11 based on a 0.05ml conversion factor and a cost per cycle of £13.45 based on an average monthly dose of 121.75 (two drops per day in each eye). B) Generic timolol/brinzolamide10mg/5ml, with a [redacted] market share, cost per drop of £0.03, leading to a cost of £3.86 per cycle based on an average monthly dose of 121.75 (two drops per day in each eye)."	Typographical error, inaccurate labelling, and inconsistent reporting.	Thank you, report amended as suggested.

On page 82: "Considering a threshold value of a QALY of £20,000, NL was cost-effective, in the SW quadrant of the CE plane compared to Trav-Tim, Lat-Tim, Tar-Tim, Bim-Tim and Brim-Tim, with ICERs over £20,000."	The company propose the wording on page 82 is edited to read: "Considering a threshold value of a QALY of £20,000, NL was cost-effective, in the SW quadrant of the CE plane compared to Trav-Tim, Lat-Tim, Taf-Tim, Bim-Tim and Brim-Tim, with ICERs over £20,000."	Typographical error.	Thank you, report amended as suggested.
On page 84: "In the revised submission post clarification queries, netarsudil-latanoprost was the third least effective of all treatments in terms of QALYs accrued, only achieving QALY gains compared to Trav-Tim and Lat-Tim. Netarsudil-latanoprost had lower costs compared to all FDCs,"	The company propose the wording on page 84 is edited to read: "In the revised submission post clarification queries, netarsudil-latanoprost was the third least effective of all treatments in terms of QALYs accrued, only achieving QALY gains compared to Trav-Tim and Lat-Tim. Netarsudil-latanoprost had higher costs compared to all FDCs,"	Inaccurate wording.	Thank you, report amended as suggested.

Issue 2 Clarifications and corrections in the text

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On pages 17-18: "In general, the baseline demographic characteristics were similar between the	The company propose the wording on pages 17-18 is edited to read: "In general, the baseline demographic characteristics were similar between the	As reported in Table 7 of the original submission, the percentage of males was 56.6% while the percentage of females	Thank you, report amended as suggested.

groups apart from sex; there were more females (60.1%) than males (39.9%) in the netarsudil-latanoprost group but similar proportions in the comparator group (51.9% and 48.1%, respectively)."	groups apart from sex; there were more females (60.1%) than males (39.9%) in the netarsudil-latanoprost group but there were more males (56.6%) than females (43.4%) in the comparator group ."	was 43.4% in the bimatoprost-timolol group.	
On pages 23-24: "A greater proportion of participants in the netarsudil-latanoprost group discontinued study treatment due to TEAEs than the bimatoprost-timolol group. This was reported in Document B, Table 27 of the CS as [redacted] in the netarsudil-latanoprost group and [redacted] in the bimatoprost-timolol group. Section B.2.10.7 of the CS refers to discontinuations of treatment due to TEAE as [redacted] of the netarsudil-latanoprost group. There are similar disparities reported in the CSR (Tables 5 and 14) thus the actual number of treatment discontinuations due to TEAEs in the netarsudil-latanoprost group is unclear to the EAG."	The Company propose that the wording on pages 23-24 is edited to read: "A greater proportion of participants in the netarsudil-latanoprost group discontinued study treatment due to TEAEs than the bimatoprost-timolol group. This was reported in Document B, Table 27 of the CS as [redacted] in the netarsudil-latanoprost group and [redacted] in the bimatoprost-timolol group for the safety population. Section B.2.10.7 of the CS refers to discontinuations of treatment due to TEAE as [redacted] of the netarsudil-latanoprost group for the randomised population."	The percentage of patients that discontinued study treatment due to TEAEs, reported as [redacted] in the netarsudil-latanoprost group and [redacted] in the bimatoprost-timolol group, was based on the safety population. Discontinuation of treatment due to TEAEs, reported as [redacted] in the netarsudil-latanoprost group and [redacted] in the bimatoprost-timolol group, was based on the randomised population, which included all patients who were randomised to treatment.	Thank you, report amended as suggested.

On page 36: "In the updated review SLT and two concomitant monotherapy regimens (brinzolamide and travoprost, brimonidine and timolol) were included in the network diagram before being dropped for reasons that were not clearly stated."	The Company propose that the wording on page 36 is edited to read: "In the updated review SLT and two concomitant monotherapy regimens (brinzolamide and travoprost, brimonidine and timolol) were excluded from the network diagram as the interventions from the studies did not directly connect to form a closed loop and hence, excluding them would not change the comparative efficacy estimates."	Reasons for the removal of the two concomitant monotherapy regimens is detailed on page 12 of the clarifications document. The studies identified with the respective comparators were excluded from the network as per the advice of an external statistical expert. Exclusion of the studies would not change the comparative efficacy estimates as they did not provide a feedback loop.	Not a factual inaccuracy, no change made. No change made. Other "dead end" treatments such as brimonidine-timolol were not dropped from the network meta-analysis. Therefore, the EAG believes that the process for including treatments is not fully transparent.
On page 54: "The company state that a scenario analysis is provided that aligns the populations between the MERCURY 3 and comparator trials by removing OHT."	The company propose the wording on page 54 is edited to read: "The company state that a scenario analysis is provided that aligns the populations between the MERCURY 3 and comparator trials in the ITC when calculating relative treatment effects, by removing OHT patients from the MERCURY 3 patient-level data. Implementing this scenario does not impact the transitions for netarsudil-latanoprost or bimatoprost-timolol – only the remaining FDC comparators."	This scenario analysis refers to adjustment to the MERCURY 3 patient-level dataset during the ITC sensitivity analyses in the original submission. The scenario impacts the transition probabilities for all comparators except netarsudil-latanoprost and bimatoprost-timolol, for which efficacy was derived directly from MERCURY 3 patient-level data.	Not a factual inaccuracy. However, the EAG appreciates the additional clarification and has updated the report to improve clarity.
On page 40: "The modelling approach of all 20 identified studies in terms	The company propose the wording on page 40 is edited to read:	Statement is inaccurate and outdated.	Thank you, report amended as suggested.

of IOP is described in Appendix A, Tables 59 and 60 of the company response to clarification questions.”	"The modelling approach of the additional 18 studies in terms of IOP is described in Appendix A, Tables 59 and 60 of the company response to clarification questions. The initial 2 studies are described in Table 26 in Appendix G of the original submission."		
On page 54: “The EAG are unclear as to how this analysis has been implemented, whether they impact on transition probabilities in the model and further note that such a scenario analysis has not been provided using the company’s updated post-clarification economic model. The EAG consider this an important consideration and would appreciate additional scenario analyses exploring the impact on cost-effectiveness of patients with OHT or POAG.”	The company propose the wording on page 54 is edited to read: “The EAG are unclear as to how this analysis has been implemented, whether they impact on transition probabilities in the model. The EAG note that such a scenario analysis could not be provided for the company’s updated post-clarification economic model due to methodological reasons. In an NMA, PLD is not matched so the previous analyses and subsequent sensitivity analyses could not be performed.”	Wording is an inaccurate reflection.	Not a factual inaccuracy. However, the EAG appreciates the clarification and has amended the wording as follows to improve clarity: *The EAG are unclear as to how this analysis has been implemented, and whether it impacts on transition probabilities in the model. The EAG further notes that this scenario analysis was not provided using the company’s updated post-clarification economic model. Post factual accuracy check, the company clarified that it was not possible to provide this scenario*

			because it was not possible to match patient level data in the NMA.
On page 56: "The company submission was unclear with regards to the dosing assumptions used for the remaining seven comparators (brinzolamide-timolol; dorzolamide-timolol; brinzolamide-brimonidine; brimonidine-timolol; latanoprost-timolol; travoprost-timolol; and tafluprost-timolol) in the economic model."	The company propose the wording on page 56 is edited to read: "The dosing details and assumptions for the remaining seven comparators are detailed in Table 52 of the original submission".	The company detailed the dosing details for the seven remaining comparators in Table 52 of the original submission.	Thank you, report amended as suggested.
On page 65: "Treatment discontinuation increases QALYs due to a reduction in adverse events, but without any loss in effectiveness (increase in IOP) for those who discontinue treatment."	The company propose the wording on page 65 is edited to read: "Treatment discontinuation marginally increases QALYs (on average across all treatments, a 20% increase in the discontinuation HR leads to a [redacted]% [min: [redacted]%, max: [redacted]%] change in lifetime QALYs) due to a reduction in adverse events, but without any loss in effectiveness (increase in IOP) for those who discontinue treatment."	The EAG statement is not supported with fact and can therefore be interpreted to be an issue with significant model impact. Through testing the model outputs, it is shown that: • Discontinuation can be excluded through setting all treatments inclusion of persistence to "No" for each health state. Overall, this impacts treatments total QALYs, on	Not a factual inaccuracy. The EAG refer the company to the following paragraph where a worked example illustrates the magnitude of impact on results.

		average by -[redacted]% (min: -[redacted]%, max: -[redacted]%). • Discontinuation can be reduced through setting the severity HR for 1.20 for all treatments. Overall, this impacts treatments total QALYs, on average by -[redacted]% (min: -[redacted]%, max: -[redacted]%). • Discontinuation can be increased through setting the severity HR for all treatments. Overall, this impacts treatments total QALYs, on average by [redacted]% (min: [redacted]%, max: [redacted]%). The company request that the EAG do not use the values in the "Description of proposed amendment", as our base case settings used to produce these values may differ to those the EAG conclude.	
On page 71: "The updated costs make reference to additional data available to the company	The company propose the wording on page 71 is edited to read: "The updated costs refer to data from the bottle quality report provided by the	The drop size of 0.035 ml for netarsudil-latanoprost is supported by results from the bottle quality report provided. Similar data is not available for the	Not a factual inaccuracy, no change made.

suggesting a smaller drop size for netarsudil-latanoprost of 0.035 which they suggest may further reduce the treatment acquisition costs of netarsudil-latanoprost."	company which reports an actual drop size of 0.035 ml."	bottles of all other treatments, so the best available evidence was used for other treatments which involved drop conversion.	
On page 70: "2) The use of BNF costs in the model implicitly assumes that the company wish to consider the use of treatments in primary care. The EAG's clinical expert view is that FDC comparators are usually initiated in secondary care but managed and prescribed routinely in primary care. However, this may differ across the country and the EAG would welcome further engagement with the clinical community on the most appropriate prescribing setting. Should it transpire that treatment is mostly prescribed in secondary care, then eMIT prices would be more appropriate."	The company propose the wording in page 70 is edited to read: "2) As demonstrated by the market share data, which was retail pharmacy level data, that informed and was used in the model, FDCs are routinely prescribed and dispensed in primary care e.g., on analysis of COSOPT UD unit data using wholesale supplier data, [redacted]% of the usage of COSOPT UD was in retail pharmacy with [redacted]% in hospitals. Consequently, the use of BNF in the model, which reflects the use of treatments in primary care, is based on data and reflective of real-world practice."	Statement is incorrect and not reflective of the evidence package provided previously.	Not a factual inaccuracy. The data provided here, at FAC were not adequately referred to in the company submission or clarification response, with respect to primary vs. secondary care prescribing. However, the EAG has now acknowledged these data in the report to improve clarity. The EAG and company are both in agreement that treatments are mostly prescribed in primary care.

On page 73: "Furthermore, the company argue that the LiGHT trial reflects the costs in a treated cohort but have applied the costs to both treated and untreated proportion of the cohort in the economic model."	The company propose the wording on page 73 is edited to read: "In line with the model structure, where all patients are treated, costs from the LiGHT trial for treated patients, are applied in the model."	Inaccurate description of the model structure and consequent misplaced criticism.	Statement removed. This statement was based on the originally submitted model and has been removed.
On page 74: "Regarding SLT treatment costs, the reference (Gazzard et al. 2019)[52] indicates the total cost of a SLT is likely to be between £96 and £151 depending on the assumptions made, with the company opting to apply the upper estimate of £151 per patient for a SLT to use the more conservative estimate.[35]"	The company propose the wording on page 74 is edited to read: "Regarding SLT treatment costs, the reference (Gazzard et al. 2019)[52] indicates the total cost of a SLT is likely to be between £96 and £151 depending on the assumptions made, with the paper selecting the conservative estimate of £151.[35] The company follow this approach."	Inaccurate description of the source material.	Not a factual inaccuracy, no change made.

Issue 3 Incorrect numerical reporting

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In the economic model, the EAG amendment of the model time horizon made by editing a non-user-editable cell introduced errors in	The company require all values to be updated in line with the corrected economic model uploaded to the NICE portal.	A negative market share value is not reflective of the real-world and an error free model should be used for reporting.	The EAG thank the company for this clarification and identification of formulae

subsequent calculations. As a result, the market share for patient's post-discontinuation included negative percentages and accounts for market shares beyond the modelled time horizon. This issue impacts the cost estimates for post-discontinuation treatment costs. Throughout the report, all results and costs reported from the excel model should be updated in alignment with the corrected excel.		The company's correction to the model has ensured that the market share calculations are dynamic and able to respond to a change in the time horizon – see changes to formula in the Discontinued patient distribution section of the Data Store. Changes also mean that market share values for years which exceed the time horizon of the CEM are not included in the analysis.	errors in the company's model. The EAG would anticipate that economic models submitted by companies should allow for sufficient sensitivity analyses around the model time horizon. However, the EAG agrees that it is important to include the corrected figures, based on the company's provided model correction. Results tables that implement scenarios using a shortened time horizon have been updated accordingly (i.e., Table 2 and Table 25). The implications of these amendments on results are minimal and don't change overall conclusions.
Within Table 25, page 103, the table presenting scenarios for the CEM is incorrect for the heading description of scenario 6, and therefore subsequently	Following agreement to the amendments made in Issue 7, the values for all scenarios should be updated, with special care taken for scenario 6 or the scenario	The company suspects that the EAG have left the switch for the drop size option set to "No".	Not a factual inaccuracy. Scenario 6 incorporates EAG preferences for AEs,

scenarios 7 and 8 are also incorrect.	description to be updated in line with the model settings used to derive results.		ml/drop conversion factor, drug tariff prices and a 1-year time horizon. The labelling on scenario 6 has been updated to improve clarity.

Issue 4 Text to be removed

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 34: "A correlation between these time points of 0.5 was assumed in this calculation but no reference was provided to justify this assumption." On pages 36-37: "In addition to needing to average results from different times of day and to impute of SDs from other studies, for some studies the company had to use simulations to derive useable data using an assumption about the correlation between baseline	The Company propose the wording on page 34 and pages 36-37 be removed.	A correlation of 0.5 was not used to simulate the mean percentage change in IOP from baseline in the specific studies. The absolute IOP at baseline and at three months were simulated independently, so correlation was not utilised.	We accept that the clarification response did not mention the reason for the correlation, but the description on p.26 does not make the reason for using this correlation clear. Therefore, we still think it is right to highlight this. On p.34 of the EAG report we have removed "between these time points" from this sentence. On p.36-37 we have removed "using an assumption about the correlation between baseline and follow-up

and follow-up values for which no justification was provided."			values for which no justification was provided" from this sentence.
On page 69: "The EAG does not agree that patient's commencing a new line of treatment will have built up brand loyalty for an FDC treatment as they have not yet experienced it."	The company propose that this should not be stated within the report.	As presented below within Issue 4, generics make up a tangible proportion of the market. The existing EAG statement suggests that, due to the high levels of discontinuation within the field, and the older age of the population, that there should be a trend in sales statistics of branded product demand falling significantly. For example, when analysing the PI publication data from January 2016 to December 2022, and excluding those treatment categories where products are either 100% generic or 100% branded, trends show that branded products, on average, have only fallen in market share across all products by [redacted] After the initial decline in market share upon introduction of generics, the market share stabilises and presents a consistent pattern, illustrating the preference for clinicians to	Not a factual inaccuracy. No changes made to this sentence. However, please see response to issue 7 below.

		continue the use of certain presentations. For example, in the dorzolamide/timolol class, the market share for branded and generics from January 2022 to December 2022 consists, on average, of [redacted] generics and [redacted] branded. In 2021, the market share, on average, consisted of [redacted] generics and [redacted] branded. This has been a consistent pattern in market shares for several years after the introduction of the generic and the initial decline of the branded treatment. *This value excluded Brinzolamide & Timolol as it is a two-product treatment group which has shown a significant shift.	
On pages 72-73: "The EAG does not consider it appropriate to include weighted average comparator costs based on market shares of branded and generic alternatives. Should the committee prefer an analysis	The company propose the wording on pages 72-73 to be removed.	The inclusion of weighted average comparator costs based on market shares of branded and generic alternatives is supported by market share data and is reflective of the evidence provided. Market share data shows that there is continued	Text has been amended in line with response to issue 7 below. The EAG clarifies that we are not disputing the company's market share

where prescriptions for glaucoma are issued in primary care, then the use of BNF costs are appropriate, but they should be based on generic substitution and use of the lowest available drug tariff price. The EAG does not agree that patient's commencing a new line of treatment will have built up brand loyalty for an FDC treatment as they have not yet experienced it. The EAG is not suggesting that patients already treated with a branded alternative should have their treatment stopped, that would be an issue for their treating clinicians to discuss with patients directly. However, for new patients, to whom NICE guidance for netarsudil-latanoprost would apply, the EAG view is that generic substitution should be applied for costing purposes. In the example of brinzolamide-timolol above, this would result in a reduced treatment acquisition cost of £3.86 per cycle."		usage of branded treatments, and that the market share for branded products show a decline upon the introduction of generics before remaining at a level where there is consistent usage of branded and generic treatments.	data but prefer the use of drug tariff pricing. This is in line with the EAG analyses in chapter 6. Text has been updated to improve clarity.

On page 75: "It is unclear whether resource use (e.g., frequency of ophthalmology appointments to manage AEs) is obtained from UK clinical expert opinion, literature, or other sources."	The company propose this statement be removed, or replaced with: "Resource use (e.g., frequency of ophthalmology appointments to manage AEs) is obtained from UK clinical expert opinion."	Inaccurate description. Contrary information provided in submission and EAG questions: "For each AE included in the model (those that occurred in ≥5%, as described in section B.3.3.3), the resource use required (e.g., the type and frequency of medical appointment) was informed by UK clinical expert input." Table 58: "resource use is informed by UK clinical expert input"	Thank you. Text reworded and adapted to improve clarity. The EAG's concern here is that it is unclear whether the adverse event treatment costs, informed by company sought clinical expert opinion, are generalisable across the UK.
On page 105: "Overall, the EAG considers the company's NMA results to be highly uncertain and there is insufficient evidence provided to assume equal equivalence across all treatment comparators."	The company propose the wording on page 105 is edited to read: "Overall, the EAG considers the company's NMA results to be highly uncertain."	The efficacy of comparators, following the NMA, is based on IPD or literature for all comparators except Brinzolamide-timolol and Tafluprost-timolol. For these comparators, assumptions of equivalence are made only within class, where the mechanism of action is equivalent.	Not a factual inaccuracy. However, the EAG understands where there could be misinterpretation of the text and has updated as follows to improve clarity: *Overall, the EAG considers the company's NMA results to be highly uncertain. There is*

			insufficient evidence to determine whether all treatments can be considered as providing similar clinical outcomes, and the NMA results do not rule out clinically meaningful differences."

Issue 5 Literature search

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 39: "The EAG suggested several studies in the literature that had not been captured by the company's searches."	The company propose the wording on page 39 is edited to read: "The EAG suggested several (16) studies in the literature that had not been captured by the company's searches, most of which (13) were excluded in line with the SLR extraction criteria for population and treatment limits. Three studies were, however, missed initially due to the date restriction but were captured as part of the TLR."	Statement is inaccurate and outdated.	Not a factual inaccuracy. Slight amendment made to the text to further clarify that the comment related to the original review.
On page 40: "Following a screening process, 18 additional publications were included, leading to a total of 20 cost-effectiveness studies identified	The Company propose that the wording on page 40 is edited to read: "Following a screening process, 18 additional publications were included, leading to a total of 20 cost-effectiveness studies identified from the original and	A total of seven cost-effectiveness studies in the UK were identified, two of which were identified from the SLR and five of which were from the TLR.	Thank you. Text amended as suggested.

from the original and (post-2017) and updated (pre-2017) targeted searches. These include 5 studies in the UK."	(post-2017) and updated (pre-2017) targeted searches. These include seven studies in the UK."		
On page 40: "The modelling approach of all 20 identified studies in terms of IOP is described in Appendix A, Tables 59 and 60 of the company response to clarification questions."	The Company propose that the wording on page 40 is edited to read: "The modelling approach of the 18 studies identified in the TLR in terms of IOP is described in Appendix A, Tables 59 and 60 of the company response to clarification questions. The two studies identified in the SLR are described in Table 26 in Appendix G of the original submission."	The studies identified in the SLR were presented in Appendix G of the original submission, while the studies identified in the TLR were presented in Appendix A of the clarification response.	See response to issue 2 above.
On page 40: "Similarly, to the issues raised in the Chapter 3 critique, the EAG note that the review of cost-effectiveness studies was also targeted, and not systematic. As such, some relevant studies may have been missed during the company's screening processes. Despite these concerns, the EAG is satisfied that the revised literature search provides enough studies from which to inform	The Company propose that the wording on page 40 is edited to read: "The EAG note that the review of cost-effectiveness studies was systematic in all elements barring the restriction of publication dates, which was post-2017 in the original search and pre-2017 in the updated search."	The literature searches for both the original SLR and updated TLR were conducted systematically, with the exception of a restriction on publication date. This was post-2017 in the original SLR search and pre-2017 in the updated TLR search. The pre-2017 searches were targeted searches but post-2017 searches were fully systematic.	Not a factual inaccuracy. No changes made.

an appropriate model structure for the current assessment.”			
On page 41: “It is unclear to the EAG how the studies in Table 12 were identified and selected. Some of the studies appear to be cost-effectiveness analyses, economic models, but others are literature reviews and guideline documents. Furthermore, the EAG disagrees with the company’s assessment of how the reported IOP thresholds in the quoted economic evaluation studies in Table 12 of the response document support their chosen model structure. The EAG considers it more appropriate to consider the relevance of all the economic evaluation studies identified in the company’s updated review and how they match the NICE reference case. The company has not provided an assessment of the relevance of all the retrieved economic evaluation studies, and it is unclear how economic	The Company propose that the wording on page 41 is edited to read: “The studies in Table 12 were identified from the original searches, updated searches, as well as additional targeted searches to identify any publications which define a mapping between IOP and glaucoma disease progression.”	The studies in Table 12 were identified from the economic evidence as identified during the original SLR and updated TLR (conducted in response to EAG clarification questions). Studies identified from the original and updated searches were selected from inclusion using the SLR criteria as previously defined. Additionally, ad-hoc searches were conducted to identify publications which define a mapping between IOP and glaucoma disease progression prior to model development. The ad-hoc searches identified six studies (Griffin 2019, Sihota 2018, Craven 2012, Musch 2012, Lai 2004, and Chen 2000) and three guideline documents (CIGT guidelines, NICE guidelines NG81, and AGIS investigators 2000).	Not a factual inaccuracy. No changes made.

evaluation studies were selected for inclusion in Table 12."			
On page 42, Table 10: The literature provided in Question B2 of the EAG questions are not included.	The company propose that the cost-effectiveness studies identified from the additional targeted searches be included in Table 10.	The nine publications (Griffin 2019, Sihota 2018, Craven 2012, Musch 2012, Lai 2004, Chen 2000, CIGT guidelines, NICE guidelines NG81, and AGIS investigators 2000) which have been identified from ad-hoc searches for studies which define a mapping between IOP and glaucoma disease progression, should be included in addition to the existing studies identified from the original (SLR) and targeted (TLR) searches.	Not a factual inaccuracy. No changes made. The results from the ad hoc searches are a mix of study types and are not all economic evaluation studies.

Issue 6 Inaccurate descriptions of economic model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page XX: "There are also no QALY losses after treatment discontinuation for lack of effectiveness, despite the company's data suggesting people who discontinue have	The company propose the wording on page XX is edited to read: "QALYs are not varied depending on treatment discontinuation, which may be due to lack of effectiveness but in most cases are due to AEs"	The sentence misrepresents the model structure, due to vague wording and the omittance of important context.	Not a factual inaccuracy. No changes made.

lower quality of life.”			
On page XIX: “The company’s economic model structure does not include any changes in transition probabilities or QALYs gained post treatment discontinuation. “	The company propose the wording on page XIX is edited to read: “The company's economic model structure applies extrapolated transition probabilities and consistent QALYs post-treatment discontinuation, that are not varied depending on treatment discontinuation.”	Inaccurate description of model and vague wording.	Not a factual inaccuracy. No changes made.
On page XIX: “However, it does assume lower treatment acquisition costs for early discontinuation because patients discontinue to generic combination treatments.”	The company propose the wording on page XIX is edited to read: “However, it does assume lower treatment acquisition costs for early discontinuation because patient’s discontinuation costs, in time, account for generic treatments. To reflect lag between discontinuation and movement to generics, there is a 16.5 cycle period post-discontinuation where patients are costed with a combination of products weighted by market share, excluding the product they have discontinued from.”	The model does not move patient who discontinue straight to generic treatments. Within the excel model, see ‘Discontinued patient costs’ section of the Cost Inputs sheet.	Not a factual inaccuracy. However, “over time” added to end of sentence to improve clarity.
On page 48: “No. Whilst a lifetime model horizon is implemented, the model structure does not capture all the important long-term cost and utility	The company propose the wording on page 48 is edited to read: “Partly. Whilst a lifetime model horizon is implemented, the model structure does not	Inaccurate reflection of full evidence and process.	Not a factual inaccuracy. No changes made.

implications of reducing IOP because changes in IOP have not been linked to glaucoma disease progression. The economic model structure is therefore insufficient for decision making over a long-term time horizon.”	capture all the important long-term cost and utility implications of reducing IOP. In the literature and guidelines there is little consensus linking IOP and glaucoma disease progression, due to the large variation in clinically acceptable/applicable target IOP ranges between patients in clinical practice, which are highly dependent on the severity of patient condition at baseline. Due to this lack of clear link, clinician input was used to determine the link between IOP and glaucoma disease progression. The economic model structure therefore has some shortcomings for decision making over a long-term time horizon.”		
On page 61: “The company’s approach does not accurately reflect the treatment pathway described in Figures 2 and 3 of this report, where patients discontinuing from FDC therapies would often require surgery or other treatments.”	The company propose the wording on page 61 is edited to read: “The company’s approach does not accurately reflect the treatment pathway described in Figures 2 and 3 of this report, not capturing all surgeries or other treatments that discontinuing patients would require. SLT and trabeculectomy are, however, included.”	Not reflective of model structure.	Not a factual inaccuracy. No changes made. The effectiveness of SLT and trabeculectomy are not included in the model.
On page 62:	The company propose the wording on page 62 is edited to read:	Inaccurate description of the model and data.	Text updated as follows to improve clarity:

"Discontinuation also impacts on adverse events by reducing adverse event management costs (because subsequent post-discontinuation treatments have lower AE profiles)."	"Discontinuation also impacts on adverse events by altering adverse event management costs, sometimes reducing adverse events if post-discontinuation treatments have lower AE profiles."		*"Discontinuation also impacts on adverse events by reducing adverse event management costs, for example when subsequent post-discontinuation treatments have lower AE profiles, as in the case of netarsudil-latanoprost discontinuation. Treatment discontinuation slightly increases QALYs due to a reduction in adverse events, but without any loss in effectiveness (increase in IOP) for those who discontinue from treatments with higher AE rates."*
On page 66: "The EAG re-iterates the primary concern with the long-term modelling that treatment discontinuation is not aligned with OHT or POAG health state, making it difficult to provide any assessment of the face validity of the treatment discontinuation curves. For example, it might be plausible	The company propose the wording on page 66 is edited to read: "The EAG re-iterates the primary concern with the long-term modelling that treatment discontinuation is not aligned with OHT or POAG health state, making it difficult to provide any assessment of the face validity of the treatment discontinuation curves. In line with the SmPC indication and NICE scope the health states include both OHT and POAG patients. This creates some	Unfair reflection of the evidence base and model structure.	Not a factual inaccuracy. No changes made.

that patients converting from OHT to POAG would require a change in their treatment, or patients experiencing a transition to more severe glaucoma disease."	uncertainty with the possibility that patients converting from OHT to POAG may require a change in their treatment. The same is also true of patients experiencing a transition to more severe glaucoma disease."		
On page 67: "Unfortunately, these data were not suitable to be incorporated in the model because it is not appropriate to assume that severe glaucoma equates with IOP>30% reduction, moderate equates with 20-30% IOP reduction, or that mild disease equates with <20% reduction."	The company propose the wording on page 67 is edited to read: "These data were not suitable to be incorporated in the model because it is not appropriate to assume that mild glaucoma equates with IOP <20% reduction, moderate equates with 20-30% IOP reduction, or that severe disease equates with <30% reduction."	The statement contradicts descriptions elsewhere in the document.	Thank you. Text amended as follows: *"These data were not suitable to be incorporated in the model because it is not appropriate to assume that severe glaucoma equates with IOP<20% reduction, moderate equates with 20-30% IOP reduction, or that mild disease equates with >30% reduction".*

Issue 7 Economic model: comparator costing sources and dosing

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Costs for BRIMONIDINE & TIMOLOL and all results within the report will require	The company have updated the cost for COMBIGANEYEDROPS15ML as this was incorrectly costed. See 'Data store', Section	The company's original and post-EAG submission contained a typographical	The EAG appreciate that the company have flagged this minor error in

updating due to errors in the original model.	'Appendix A' for the update units from 5 to 15. The description has also been updated to COMBIGANEYEDROPS15ML (3*5ml).	error which impacted calculation throughout the model. The units per pack was incorrectly reported, leading to an overestimation of price.	their costing approach for brimonidine- timolol. This is not a factual inaccuracy on the EAG's part. However, it is important for consistent and correct results to be reported. The EAG have therefore updated the relevant report tables. The implications on results are minimal and lead to no changes in overall conclusions.
On page XXI: "The company's preferred approach to costing relevant comparators assumes an average market share of branded and generic products within class, prescribed in primary care."	The company propose the wording on page XXI is edited to read: "The company's preferred approach to costing relevant comparators uses product-specific market shares to guide the balance between branded and generic products within class, prescribed in primary care". "The lowest generic, drug tariff price, from the BNF is applied for the generic products, while the NHS indicative price is applied for branded products, with a weighted cost calculated based on market shares"	Wording is vague and unreflective of the model; implying assumptions were made on market shares when these were based on published data from IQVIA: NATSCM_UK_M_SCM (Supply Chain Manager) Monthly Reports S01E Miotics+ Antiglaucoma prep. This dataset reports what presentations are being	The edits suggested in the first paragraph have been implemented in the executive summary. The additional context requested in paragraph 2 is available from the main body of the report.

		used at retail pharmacy level. Extra context is required to contextualise the point.	
On page XXII: "The EAG prefers to use the lowest generic, drug tariff price, from the BNF for prescribing in primary care, or the eMIT price for secondary care prescribing as this more accurately reflects the likely prescribing in clinical practice going forward." Subsequently to the above, results are reported in line with the EAGs approach to drug costs.	The company propose the wording on page XXI is edited to read: "The EAG accepts the company's pre-defined pricing using a mixture of drug tariff prices and NHS indicative prices. For additional perspective, the EAG also provides an alternative scenario of eMIT prices, which represents a secondary care prescription only situation." The company request that the EAG state why their costing approach is their preference as this appears to be based on assumption, as opposed to the company base case which is based on data from IQVIA: NATSCM_UK_M_SCM (Supply Chain Manager) Monthly Reports S01E Miotics+ Antiglaucoma prep. This dataset reports what presentations are being used at retail pharmacy level. On average 95% of dispensing for glaucoma products occur at retail pharmacy levels. The company suggest the EAG review the reference provided for the "2022 class MS" in the Data Store of the excel model.	In line with above inaccuracy of description, part of the recommendation is no longer relevant. Presently, changing cost perspective and subsequent results are misleading presented as fact, not EAG opinion.	The quoted text is now updated as follows: *"The EAG prefers to use drug tariff prices in the base case analysis, obtained from the BNF, if prescribing typically takes place in primary care."* The EAG has now provided further clarification regarding the preferred costing assumptions, and updated text in several sections of the report (executive summary, section 4.2.8 and chapter 6) to ensure the text accurately describes the EAG preferred analyses. These updates include: 1) Making clear that whilst generic substitution is a

			relevant analysis to consider, it is not the EAG's base case. 2) The EAG's base case analysis used drug tariff pricing for prescriptions in primary care but maintained the company's market share distribution of treatments within class.
On page 68: "For all treatments, the calculated cost per drop was then multiplied by the frequency of use per cycle (60.88 drops), enough to treat both eyes once per day), leading to a total treatment acquisition cost per monthly model cycle of £14.51 for netarsudil-latanoprost."	The company propose the wording on page 68 is edited to read: "Based on the SmPC recommended dose, the cost per drop was multiplied by the frequency per cycle (60.88 or 121.75 drops) leading to a total treatment acquisition cost per monthly model cycle. For netarsudil-latanoprost, which has 60.88 drops in the model, this cost is £14.51."	Unreflective wording for model.	Not a factual inaccuracy. However, text is updated as suggested to improve clarity.
On page 68: "The updated costs make reference to additional data	The company propose the wording on page 68 is edited to read: "The updated costs reference to additional data from a report assessing the drop size and dosage,	Unreflective description of evidence and methodology.	Not a factual inaccuracy. No changes made.

available to the company suggesting a smaller drop size for netarsudil-latanoprost of 0.035 which they suggest may further reduce the treatment acquisition costs of netarsudil-latanoprost. “	which reports a smaller drop size of netarsudil-latanoprost of 0.035 in practice. This is applied in the model for calculation of treatment acquisition costs. “		
On page 73: “For example, in the case of the generic "Dorzolamide/timolol eye drops 2% 60.2ml," the company approach to costing assumes that the cost of the branded product COSOPT "COSOPT EYEDROP U/D 60.2ML" for NHS indicative pricing at £28.59 and drug tariff pricing at £17.86. Assuming the cost of a branded treatment for the proportion of patients receiving a generic alternative based on market share data biases the company’s costing in favour of netarsudil-latanoprost in the model.”	The company propose the wording on page 73 is edited to read: “For all but two products, the company has assumed that generic products use the drug tariff price, and branded products to use the NHS indicative price. In the case where costs have not been available for either drug tariff or indicative, “DORZOLAMID/TIMOLOLEYEDROPS2%60.2ML” and “COMBIGANEYEDROPS35ML”, the company has assumed costs to be equal to alternatives. For “DORZOLAMID/TIMOLOLEYEDROPS2%60.2ML”, the alternative 60.2ML cost available only for “COSOPTEYEDROPU/D60.2ML” has been used. In the base case, the lower drug tariff price is selected. For “COMBIGANEYEDROPS35ML”, a 35ml cost was not available, so a 15ml cost alternative has been used.” The use of a cost of a branded treatment for the proportion of patients receiving a generic	Throughout costing, it is consistent for generic products to use the drug tariff and branded products to use the NHS indicative price – within the model see columns E and M of the cost table in Appendix A. The current text leads the reader to believe this rule has been regularly disregarded, the reality is two products. The percentage in the proposed amendment is valued through: - Current value: £6.52 - Updated value: £5.60	Not a factual inaccuracy. No changes made. However, the EAG acknowledges the additional clarification provided by the company and refers to responses to other issues which now clarify the assumptions regarding branded vs. generic prescribing.

	alternative based on market share data biases the company's costing in favour of netarsudil-latanoprost in the model. Amendment of this assumption to instead be equal to the average of other generic products within the "DORZOLAMIDE & TIMOLOL" active ingredient category, increases the average cost per cycle for "DORZOLAMIDE & TIMOLOL" by 16.4%.		

Issue 8 Economic model: modelling the fellow-eye

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 55: "They noted that a previous pharmaceutical company, Aerie®, conducted the MERCURY 3 study and wrote the clinical study report (CSR) without clearly specifying which eye was designated as the study eye. However, the company's assessment of the IPD data from MERCURY 3 suggests that the study eye was likely to be the 'worst-seeing eye'. In response to clarification, the	The company propose the wording on page 55 is edited to read: "They noted that a previous pharmaceutical company, Aerie®, conducted the MERCURY 3 study and wrote the clinical study report (CSR). The Stalmans et al. 2023 publication clarifies that the selection of study eye was dependent on the eye with the higher IOP (the worst seeing eye). In response to clarification, the company added a switch to the economic model to allow transition probabilities to follow	See justification above.	Text amended as suggested.

company added a switch to the economic model to allow transition probabilities to follow either the 'study' (assumed 'worst seeing') or 'fellow' (assumed 'best seeing') eye."	either the 'study' ('worst seeing') or 'fellow' ('best seeing') eye."		
On page 55: "However, when applying the switch to the 'fellow' (assumed) best seeing eye, the costs increase and QALYs decrease relative to the base case (study eye). The EAG are concerned that this output may lack a degree of face validity when assessed against what might be expected in clinical practice. It is feasible that the lack of model face validity output is a consequence of other issues raised with regards to treatment effectiveness and model structure throughout this report."	The company propose the following wording on page 55 is edited to read: "Cost and QALY differences between the study eye and fellow eye are negligible, with the study eye being marginally larger. On average across all treatments, there is a £[redacted] (min: [redacted], max: [redacted]) difference in total costs, a [redacted] (min: [redacted], max: [redacted]) difference in total life years gained, and a [redacted] (min: [redacted], max: [redacted]) difference in lifetimes QALYs."	The EAG statement regarding the model lacking face validity due to differences in costs and QALYs between the study and fellow eye are based on non-significant values. Differences smaller than <0.11% are not attributable to a model with lacking validity. The company suggest either the data presented in the proposed amendment is included to support the EAG statements, or the statements are not included in the report. The company request that the EAG do not use the values in the "Description of proposed amendment", as our base case settings used to produce these values may differ to those the EAG conclude.	Not a factual inaccuracy. Minor wording changes implemented to acknowledge that the magnitude of bias is small.

On page 58: “The EAG are concerned that the company have not been able to accurately identify whether the study eye included in the model is the one with ‘best’ or ‘worst’ sight and have instead relied on assumptions from their data.”	On page 58, remove the following statement: “The EAG accept concerned that the company have not been able to accurately identify whether the study eye included in the model is the one with ‘best’ or ‘worst’ sight and have instead relied on assumptions from their data.”	The desired missing information is provided in an additional source: “The study eye was the eye with the higher IOP at 08:00 h on Visit 3; if both eyes had the same IOP at this visit, then the right eye was determined the study eye”. **Reference (to be added to reference pack):** Stalmans, Ingeborg, Kin Sheng Lim, Francesco Oddone, Marek Fichtl, Jose I. Belda, Anton Hommer, Guna Laganovska et al. "MERCURY-3: A randomized comparison of netarsudil/latanoprost and bimatoprost/timolol in open-angle glaucoma and ocular hypertension." *Graefe's Archive for Clinical and Experimental Ophthalmology* (2023): 1-12. Available from: https://link.springer.com/article/10.1007/s00417-023-06192-0	Not a factual inaccuracy in the EAG report. However, the text is updated to acknowledge the further information provided by the company.

Issue 9 Economic model: HRQoL and QALYs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 48: "Partly. Health effects whilst on treatment are measured using QALYs, derived from EQ-5D. However, it is assumed that discontinuing treatment does not impact on IOP, or hence QALYs. The EAG considers that there may be QALY benefits of slowing disease progression or avoiding need to move to subsequent lines of treatment that are not captured in the model"	The company suggest the wording on page 48 be edited to read: "Partly. Health effects whilst on treatment are measured using QALYs, derived from EQ-5D. However, expert clinical opinion informed that discontinuing treatment does not impact on IOP, or hence QALYs, as prior treatment is not a treatment effect modifier. The EAG considers that there may be QALY benefits of slowing disease progression or avoiding need to move to subsequent lines of treatment that are not captured in the model".	Inaccurate reflection of evidence base.	Not a factual inaccuracy. No changes made.
On page 49: "Scenario analyses requested by the EAG to use SF-6D utilities in the model were not provided and information provided on SF-6D utilities were inaccurate. Scenario analyses applying published utilities for glaucoma health	The company propose the following wording on page 49 be edited to read: "Scenario analyses requested by the EAG to use SF-6D utilities in the model were not provided, as the company considered the current mapping and three alternative QoL literature sources to be sufficient and more appropriate. The company instead provided information on the mean values	Accurate SF-6D mean values were provided in B10 of the clarification response. SF-6D utility values were not provided, as was stated in the clarification response, as the company considered that the usage of the alternative QoL literature	Not a factual inaccuracy. The EAG requested SF-6D utilities and sensitivity analysis. The company did not provide what was requested.

states to health states defined based on percentage changes in IOP from baseline are not appropriate for decision making.”	of SF-6D to validate the usability of the data and trends.” Scenario analyses presented by the company used alternative health state utility values. One scenario showed that through increasing health state utilities, by an average of [redacted]% (<20% IOP, [redacted]%. 20-30% IOP [redacted]%. >30% IOP, [redacted]%), lifetime QALYs across all treatments increased, on average, by [redacted]. A second scenario showed that through decreasing health state utilities, by an average of [redacted]% (<20% IOP, [redacted]%. 20-30% IOP [redacted]%. >30% IOP, [redacted]%), lifetime QALYs across all treatments decreased, on average, by [redacted] However, the EAG consider that applying published utilities for glaucoma health states to health states defined based on percentage changes in IOP from baseline are not appropriate for decision making.”	sources were sufficient and more appropriate. Furthermore, the discussion on scenario analyses should be supported with fact when evaluating the suitability of applying published utilities for glaucoma health states to health states defined based on percentage changes in IOP from baseline. The company request that the EAG do not use the values in the “Description of proposed amendment”, as our base case settings used to produce these values may differ to those the EAG conclude.	

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Netarsudil-latanoprost for previously treated open-angle glaucoma or ocular hypertension [ID1363]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Monday 22 January 2024**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Santen UK&I
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

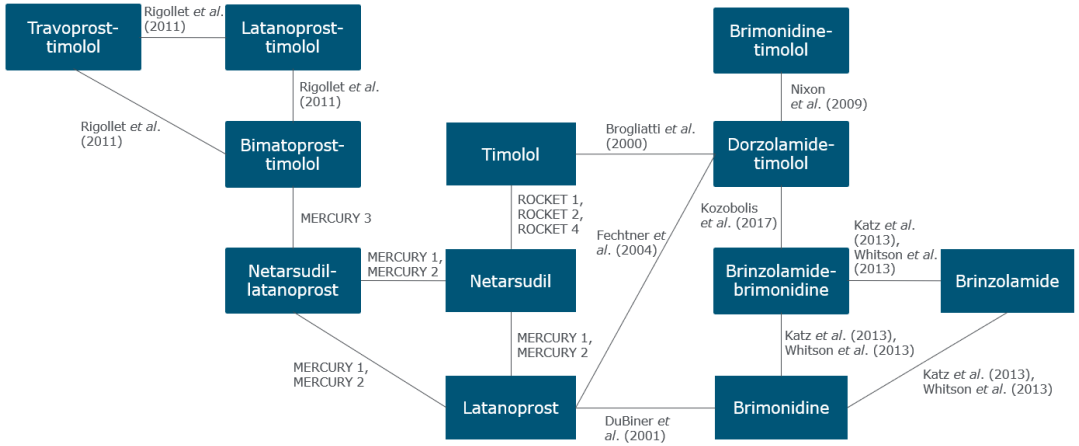
All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1: Non-systematic inclusion of monotherapy trials the network meta-analysis	Yes	The NMA submitted in response to the EAG clarification questions undertook a pragmatic approach. The pragmatic approach was undertaken to enable the development of a connected network of evidence in the short time available to respond to the EAG clarification questions. As there was a disjoint network of evidence for the NMA, a pragmatic approach was undertaken in that the first feasible bridge of the NMA network, using monotherapy studies, was accepted to connect the network. However, the EAG has noted that the way in which the evidence was reviewed for the response to clarification questions was not systematic and may have led to bias in the results of the NMA. In response to the issue highlighted by the EAG, the Company has completed screening all of the hits from the targeted database searches conducted as part of the EAG clarification questions (see response to question A8 of the clarification questions for search methodology and results). Monotherapy studies that were extracted in the original SLR were reconsidered, to identify an alternative robust connected NMA network to that presented in the response to clarification questions, that is not reliant on a single connection via latanoprost. Subsequently, a NMA sensitivity analysis was undertaken.

Following screening, an alternative network of evidence was identified that was not reliant on a single connection via latanoprost. The network was formed using two additional studies from the targeted database searches (Brogliatti *et al*. [2000] and Fechtner *et al*. [2004])[1,2] and three studies from the original SLR (ROCKET 1, ROCKET 2 and ROCKET 4).[3(p1),4,5] The connected network of evidence of 14 RCTs that were assessed for feasibility of inclusion in the NMA sensitivity analysis is presented in Figure 1.

Figure 1: Connected evidence network



NMA feasibility assessment overview:

The assessment of feasibility of an NMA was undertaken following the same methodology outlined in the response to EAG clarification question A8. The feasibility assessment summarised below details the consideration of the five additional studies added to the evidence network (ROCKET 1, ROCKET 2, ROCKET 4, Brogliatti *et al*. [2000], Fechtner *et al*. [2004]) and the netarsudil treatment arm of MERCURY 1 and MERCURY 2 only.[1–5] For Fechtner *et al*. [2004], only study 1 was assessed since study 2 was not conducted in all western countries.

Study design heterogeneity:

		The study design of the five additional studies considered in the NMA feasibility assessment are shown in Table 20 and Table 21 in the Appendix. ROCKET 1, ROCKET 2 and ROCKET 4 were all double-blinded, multicentred trials, while Fechtner *et al*. (2004) was a multicentre observer-masked and patient-masked trial.[2–5] Brogliatti *et al*. (2000) did not report study blinding or whether it was multicentre.[1] Three studies (ROCKET 1, ROCKET 2 and ROCKET 4) were Phase 3 randomised controlled trials (RCTs) while the remaining two studies did not report the trial phase. ROCKET 1, ROCKET 2, ROCKET 4 and Fechtner *et al*. (2004) all recruited patients diagnosed with open angle glaucoma (OAG) or ocular hypertension (OHT).[2–5] Brogliatti *et al*. (2000) only included patients with primary open angle glaucoma (POAG).[1] The duration of follow-up for the RCTs varied substantially between 30 days (Brogliatti *et al*. [2000]) and 12 months (ROCKET 2).[1,3] Except for Brogliatti *et al*. (2000), who did not report the randomisation method, all RCTs used a computer-generated randomisation schedule. In summary, except for the follow-up duration, study design characteristics were largely comparable across the five additional RCTs considered. The Brogliatti *et al*. (2000) study was excluded due to study design heterogeneity for follow-up duration: the follow-up duration of this trial was 30 days, which differed significantly from the outcome of interest for the NMA – percentage change in diurnal IOP from baseline at three months.[1] Following exclusion of the Brogliatti *et al*. (2000) study, ROCKET 1, ROCKET 2 and ROCKET 4 studies were also excluded as the comparator timolol no longer formed a closed loop within the evidence network. Therefore, only Fechtner *et al*. (2004) and the netarsudil treatment arm of MERCURY 1 and MERCURY 2 were assessed further in the feasibility assessment.[2,6,7] Patient population heterogeneity: The baseline characteristics of the Fechtner *et al*. (2004) study and the netarsudil treatment arm of MERCURY 1 and MERCURY 2 are summarised in Table 22. Characteristics of the Fechtner *et al*. (2004) study largely align with the other studies in the evidence network. Fechtner *et al*. (2004) included patients aged 18 years or older and the mean baseline age in this study was 62.6 years old in the

		dorzolamide-timolol treatment arm and 63.1 years old in the latanoprost treatment arm.[2] Similarly, the mean baseline age of patients in the netarsudil arms of MERCURY 1 and MERCURY 2 were 64.6 and 64.5 years, respectively. This is comparable to the remaining studies in the network where the mean baseline age varied between 61 years and 71 years across all studies and treatment arms. Fechtner *et al*. (2004) did not report the study eye diagnosis of patients, although, as previously described in study design heterogeneity, the study recruited patients diagnosed with either OAG or OHT.[2] This aligns with all studies in the network, except Kozobolis et al. (2017), which included patients with POAG only.[8] Mean diurnal intraocular pressure (IOP) at baseline ranged between 25.6 and 26.1 mmHg across treatment arms in the Fechtner *et al*. (2004) study.[2] In both MERCURY 1 and MERCURY 2, the mean diurnal IOP was 23.6 mmHg in the netarsudil treatment arms. There is no variation in baseline IOP compared to the other studies in the network – baseline IOP varied between 23.5 mmHg and 28.2 mmHg across all studies. Similarly to all studies in the evidence network, except for MERCURY 3, Fechtner *et al*. (2004), MERCURY 1 and MERCURY 2 did not report the cup to disc ratio of patients.[2] Therefore, heterogeneity of this characteristic could not be evaluated. Prior therapy in the MERCURY 1 and MERCURY 2 trials was discussed in the previous feasibility assessment in response to EAG clarification question A8. The Fechtner *et al*. (2004) study included patients whether or not they were currently taking ocular hypotensive therapy, and regardless of how effective any therapy was.[2] Though the proportion of patients that were treatment naïve or previously treated was not reported, the proportion of patients that had IOP therapy with timolol, dorzolamide, latanoprost or other was reported. As described in the previous feasibility assessment however, previous treatment was not validated as a key treatment effect modifier or prognostic variable by a UK clinical expert.[9] Therefore, the difference in previous treatments between trials was not expected to bias the NMA results. In summary, the variation in patient population that existed between Fechtner *et al*. (2004), the Netarsudil treatment arms of MERCURY 1 and MERCURY 2 and the remaining studies in the network was minimal. Therefore, no studies were excluded due to patient population heterogeneity.

Treatment arm heterogeneity:

Since netarsudil, latanoprost and dorzolamide-timolol have been assessed in multiple studies, it was necessary to compare how these treatments were administered in the different trials to assess whether they were sufficiently homogenous. The remaining comparators that had been assessed in multiple studies and were unaffected by the newly added studies in the updated evidence network (netarsudil-latanoprost, brimonidine, brinzolamide-brimonidine and brinzolamide) were assessed in the prior feasibility assessment in response to EAG clarification question A8.

Comparability of netarsudil:

The dose and administration schedule of netarsudil across MERCURY 1 and MERCURY 2 are compared in Table 1. The dose administration and regimen were equivalent. Treatment duration varied between three months and 12 months across the two studies. However, data on IOP was reported at three months for both studies, and therefore data at an equal treatment duration of three months could be used in the analysis.

Table 1: Comparability of netarsudil treatment arms

Trial	Dose	Administration	Duration of treatment	Timing
MERCURY 1[7]	Netarsudil 0.02%	Eye drop	12 months	One drop into each eye once daily (between 8PM and 10PM)
MERCURY 2[6]	Netarsudil 0.02%	Eye drop	3 months	One drop into each eye once daily (between 8PM and 10PM)

Comparability of latanoprost:

The dose and administration schedule of latanoprost across MERCURY 1, MERCURY 2, DuBiner *et al*. (2001) and Fechtner *et al*. (2004) are compared in Table 2. Across all trials, the latanoprost dose was equivalent and administered in the evening. In MERCURY 1, MERCURY 2 and Fechtner *et al*. (2004), one drop of latanoprost was administered per day.[2,6,7] Marginal variation existed in comparison to DuBiner *et al*. (2001), where between one and two drops were administered per day.[10] Treatment duration varied between three months and 12 months. However, IOP was reported at

three months for each study, and therefore outcomes at an equal treatment duration of three months could be used in the analysis.

Table 2: Comparability of latanoprost treatment arms

Trial	Dose	Administration	Duration of treatment	Timing
MERCURY 1[7]	Latanoprost 0.005%	Eye drop	12 months	One drop once daily (between 8:00PM and 10:00PM)
MERCURY 2[6]	Latanoprost 0.005%	Eye drop	3 months	One drop once daily (between 8:00PM and 10:00PM)
DuBiner *et al*. (2001)[10]	Latanoprost 0.005%	Eye drop	3 months	One or two drops (between 7:00 and 9:00AM) and one or two drops (between 7:00 and 9:00PM)
Fechtner *et al*. (2004)[2]	Latanoprost 0.005%	Eye drop	3 months	One drop once daily (at 10PM)

Comparability of dorzolamide-timolol:

The dose and administration schedule of dorzolamide-timolol across Fechtner *et al*. (2004), Nixon *et al*. (2009) and Kozobolis *et al*. (2017) are compared in Table 3. The dose administration schedule, and treatment duration were equivalent.

Table 3: Comparability of dorzolamide-timolol treatment arms

Trial	Dose	Administration	Duration of treatment	Timing
Fechtner *et al*. (2004)[2]	Dorzolamide 2%/ Timolol 0.5%	Eye drop	3 months	One drop into each eye twice daily (8AM and 10PM)
Nixon *et al*. (2009)[11]	Dorzolamide 2%/ Timolol 0.5%	Eye drop	3 months	Twice daily (Between 7:00 AM and 8:00

					AM, between 7:00 PM and 8:00 PM)
		Kozobolis *et al*. (2017)[8]	Dorzolamide 2%/ Timolol 0.5%	Eye drop	3 months	Twice daily

In summary, minimal variation existed between treatment arms and as such, no studies were excluded due to treatment arm heterogeneity.

Outcome measure heterogeneity:

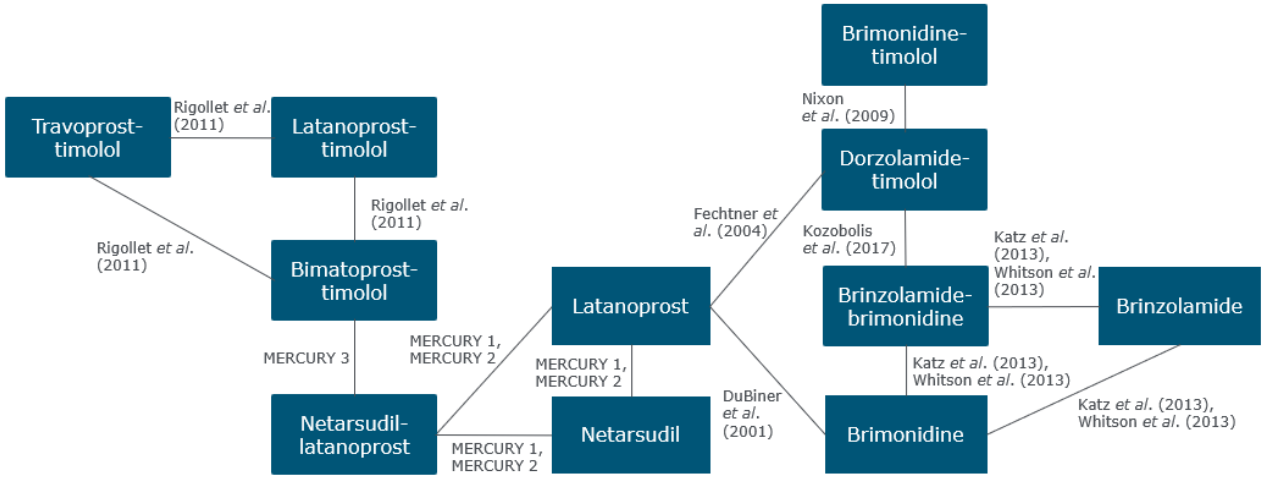
Consistent with the previous ITC analyses conducted, the outcome of interest for the NMA was the percentage change in diurnal IOP from baseline. Justification of the inclusion of this endpoint is detailed in Section B.2.9.1.2.1 in Document B of the original submission.

For the additional comparator (netarsudil) and the additional study included in the network (Fechtner *et al*. [2004])[2], IOP data was reported at baseline and a three-month time point. Aligning with the other studies in the evidence network, sufficient IOP data was reported to simulate percentage change form baseline in diurnal IOP. Therefore, no studies were excluded due to outcome measure heterogeneity.

Conclusion:

It was determined that an NMA based on the restricted evidence network (Figure 2) consisting of 10 RCTs to assess the percentage change in diurnal IOP from baseline was feasible.

Figure 2: Restricted evidence network



NMA methodology:

The same NMA methodology as detailed in the response to EAG question A8 was employed for the analysis.

For clarity, the data used in the analysis was extracted and manipulated (where required) from the pivotal publications of each study and is presented in the Appendix in Table 20 and Table 21.

For the analysis of the percentage change in IOP from baseline, the following steps were carried out:

- Relevant IOP data was extracted from the pivotal publications of each study (as summarised in Table 24).
- Where required, the data was manipulated so that each study had a diurnal mean IOP value and corresponding standard deviation (SD) at baseline and at month 3 for each treatment arm (see Table 20 and Table 21 for further information about data manipulation).
- In the NMA analysis, the baseline and month 3 diurnal IOP values and corresponding SDs were used to simulate the percentage change from baseline in diurnal IOP. As detailed in the response to question A8 of the EAG clarification questions:
    - The mean and standard deviation of IOP at baseline and month 3 as shown in Table 24 of the Appendix were loaded into R

- 100,000 samples of the baseline and post-baseline (three-month) values were simulated using mvrnorm() in R based on the mean and variance reported.
- The 100,000 paired samples were used to calculate 100,000 percentage change from baseline estimates.
- Following this, the mean and SD were calculated for the 100,000 estimates of percentage change from baseline.
- The R code used to simulate percentage change in diurnal IOP is presented in Figure 3. Further details on the variable definitions and corresponding values presented in the R code can be found in Table 25 of the Appendix.

- The resulting percentage change from baseline in IOP was analysed in the NMA (Model specifications are as detailed in the response to question A8 of the EAG clarification questions. The data input table is provided in Table 25 of the Appendix.)

Figure 3: R code for simulation of percentage change from baseline in diurnal IOP
Change y1 and se1 to y2/y3 and se2/se3 for the other two arms

```
dat<-read.csv("Data.csv")
y1<-NULL
se1<-NULL
for(i in 1:dim(dat)[1]){
  new.dat <- mvrnorm(100000, c(dat$y1_b[i],dat$y1_p[i]),
                     matrix(c(dat$se1_b[i]^2, dat$se1_b[1]*dat$se1_p[i]*0.5,
                              dat$se1_b[1]*dat$se1_p[i]*0.5,dat$se1_p[i]^2),
                            nrow=2))
  p_CFB <- (new.dat[,2]-new.dat[,1])/new.dat[,1]
  y1[i] <- mean(p_CFB)
  se1[i] <- sd(p_CFB)
}
```

NMA results:

Base case analysis (random effects model)

Results in Figure 4 show that, for the random effects analysis, patients treated with netarsudil-latanoprost had a greater percentage change in diurnal IOP from baseline compared to netarsudil, dorzolamide-timolol, brinzolamide,

brinzolamide-brimonidine, brimonidine, latanoprost and travoprost-timolol (treatment effect [95% CrI]: [redacted], respectively). Considering the comparison of netarsudil-latanoprost with netarsudil as an example, the results indicate that the reduction in diurnal IOP from baseline with patients who received netarsudil-latanoprost was [redacted] percentage points greater than for patients who received netarsudil.

Furthermore, patients treated with netarsudil-latanoprost had a lower percentage change in diurnal IOP from baseline compared to brimonidine-timolol, latanoprost-timolol and bimatoprost-timolol (treatment effect [95% CrI]: [redacted], respectively). However, the treatment effects for the comparison of netarsudil-latanoprost with all treatments are close to zero, indicating that these treatments have similar efficacy.

Consistent with the base case analysis provided during EAG clarification questions, no results demonstrated statistical significance.

Figure 4: Forest plot - percentage change in diurnal IOP from baseline (random effects model)

Abbreviations: IOP – intraocular pressure; SD – standard deviation

Scenario analysis (fixed effect model):

Results in Figure 5 show that, for the fixed effect analysis, patients treated with netarsudil-latanoprost had a greater percentage change in diurnal IOP from baseline compared to netarsudil, dorzolamide-timolol, brinzolamide,

		brinzolamide-brimonidine, brimonidine, latanoprost and travoprost-timolol (treatment effect [95% CrI]: [redacted], respectively). Considering the comparison of netarsudil-latanoprost with netarsudil as an example, the results indicate that the reduction in diurnal IOP from baseline with patients who received netarsudil-latanoprost was [redacted] percentage points greater than for patients who received brinzolamide. Furthermore, patients treated with netarsudil-latanoprost had a lower percentage change in diurnal IOP from baseline compared to brimonidine-timolol, latanoprost-timolol and bimatoprost-timolol (treatment effect [95% CrI]: [redacted], respectively). However, the treatment effects for the comparison of netarsudil-latanoprost with all treatments are close to zero, indicating that these treatment arms have similar efficacy. Consistent with the base case analysis provided during EAG clarification questions, no results demonstrated statistical significance. However, the hypothesis of no difference is central in the credible intervals of all comparisons and so it can be concluded that there is no difference in treatment effect between the different treatment strategies. **Figure 5: Forest plot - percentage change in diurnal IOP from baseline (fixed effect model)** [redacted] Abbreviations: IOP – intraocular pressure; SD – standard deviation Treatment effect was comparable between the random effects and fixed effect models. As the residual deviance and DIC were within three points for both models (Table 4), the random effects model was retained for the base case. The

between study SD was moderate, which suggests that the relative treatment effects, and thus results, are generally comparable across the studies considered.

Table 4: Key statistics for the random effects and fixed effect analyses of the treatment effect of percentage change in diurnal IOP from baseline

	Random effects	Fixed effect
Residual deviance	[redacted]	[redacted]
DIC	[redacted]	[redacted]
Between study SD	[redacted]	N/A

Abbreviations: DIC – deviance information criterion; IOP – intraocular pressure; SD – standard deviation

NMA conclusion:

The NMA analyses for percentage change in diurnal IOP from baseline show that netarsudil-latanoprost was more effective in increasing percentage change from baseline in diurnal IOP compared to netarsudil, dorzolamide-timolol, brinzolamide, brinzolamide-brimonidine, brimonidine, latanoprost and travoprost-timolol. However, the results were not statistically significant for any of the treatment comparisons. The small differences in treatment effect (less than a difference of 11 percentage points) indicate negligible differences in treatment efficacy between all therapies considered in the NMA.

In contrast to the NMA undertaken as part of the EAG clarification questions, the results of this NMA sensitivity analysis indicate that patients receiving netarsudil-latanoprost had a greater percentage change in diurnal IOP from baseline compared to dorzolamide-timolol and brinzolamide-brimonidine. Nonetheless, the results of the NMA sensitivity analysis largely align with the NMA undertaken previously with small differences in treatment effect as all treatment comparisons are close to zero and none of the differences between treatments were found to be statistically significant.

Cost-effectiveness model (CEM) scenario analysis results:

The results of the random effects and fixed effect NMA analyses were applied in the cost-effectiveness model as two separate sensitivity analyses (assessing the impact of the random effects and fixed effect results), using the same method as detailed in the response to EAG question B5. The scenario analyses were applied to the updated base case, including changes to the time horizon, discontinuation assumptions, and AE resource use assumptions as detailed in their respective issues.

		Random effects analysis: When the random effects sensitivity analysis is applied in the economic model, netarsudil-latanoprost was associated with a total cost of £[redacted] and [redacted] total QALYs (Table 19). When compared to the treatment with the lowest total costs (brinzolamide-timolol), netarsudil-latanoprost was dominated. These results are in line with the updated base case. *Fixed effect analysis:* When the fixed effect sensitivity analysis is applied in the economic model, netarsudil-latanoprost was associated with a total cost of £[redacted] and [redacted] total QALYs (Table 19). When compared versus the treatment with the lowest total costs (brinzolamide-timolol), netarsudil-latanoprost was dominated. These results are in line with the updated base case. *Conclusion:* The scenario analysis performed for this response to technical engagement enabled an understanding of the impact of moving from the pragmatic approach applied in the response to clarification questions, to a systematic approach of completing the NMA evidence network. The analysis demonstrates that the systematic approach undertaken in sensitivity analysis is consistent with the pragmatic approach. Given that the systematic approach generates more optimistic results for netarsudil-latanoprost than the pragmatic approach, the pragmatic approach has been maintained in the base case. The sensitivity analysis demonstrates that the base case is conservative with respect to the marginal differences of netarsudil-latanoprost to the other FDC therapies.
2: Economic model structure does not capture disease progression	Yes	In addressing Issues 2 and 3, The Company provide a joint response due to the adaptations to the model addressing both issues. As such a single response has been provided. To address both concerns on what happens to patients once they discontinue from their assigned treatment, and also to address concerns on the health states being used to represent a life-time horizon, it is The Company's preference to align with the EAG's request for a shorter time horizon. The Company propose that the time horizon be based on time on treatment, allowing for discontinuation to be excluded. This is considered advantageous for the development of legitimate results as it ensures that treatments are not impacted by the inputs of their comparators – i.e., when assessing a patient in the model who is in the netarsudil-latanoprost treatment arm, following discontinuation the netarsudil-latanoprost treatment arm is neither benefited nor hindered by its comparators. In the previous application of treatment post-discontinuation, it meant all treatment arms were impacted by their comparator products as the majority of a patient's time in the model was spent on a basket of products, which excluded the treatment arm's product. The impact of the ICER risked being driven more by comparator data than

treatment arm data. Furthermore, this approach reduces uncertainty and the dependence on estimates, extrapolations, and assumptions around longer-term efficacy, QoL, and the treatment pathway for discontinuing patients, for which data is limited. This negates the need to make assumptions around the efficacy of patients in the second line.

With discontinuation removed, instead of patients discontinuing to a 'second line' weighted basket comparator, all patients remain on treatment for the full length of the time horizon (base case: 12 months). This was considered suitable given the heterogeneity of time to 50% discontinuation across all the comparators, ranging from 12 to 21 cycles, and netarsudil-latanoprost at 15 cycles (see Table 5). This summary data is exclusive of data shared in the original submission for Bimatoprost and timolol's time on treatment – this product presents a median time on treatment of 102 months, significantly different to all other data in the market.

Following consultation with clinicians, it has been agreed that those patients within the Bimatoprost and timolol arm of the MERCURY 3 trial are not a representative sample of the POAG/OHT population. The CSR states that those eligible for treatment must not be treatment naïve nor present any sensitivity to investigational formulations, the latter indicating only those who tolerate bimatoprost and timolol are included – an unfair representation of the POAG/OHT population. To support this, The Company has undertaken an analysis of adverse event frequencies experienced by bimatoprost and timolol patients in MERCURY 3 versus alternative studies. Table 6 shows how the 12-month discontinuation rates of 12.26% in MERCURY 3 is lower than most alternative studies for bimatoprost and timolol.

Table 5: Time on treatment per product

Comparator class	Comparators	Market share	Cycle at which 0.50 discontinuation	Source assumption
RKI+PGA	Netarsudil-latanoprost	6.34%	15	-
CAI+BB	Dorzolamide and timolol	19.24%	21	
CAI+BB	Brinzolamide and timolol	10.80%	21	Assumed equal to dorzolamide and timolol
CAI+SYMP	Brinzolamide and brimonidine	9.35%	19	-
Symp+BB	Brimonidine and timolol	0.01%	12	-
PGA+BB	*Bimatoprost and timolol*	*46.79%*	*102*	-
PGA+BB	*Latanoprost and timolol*	*4.41%*	*102*	*Assumed equal to*
PGA+BB	*Tafluprost and timolol*	*2.86%*	*102*	
PGA+BB	*Travoprost and Timolol*	*0.20%*	*102*	

				bimatoprost and timolol

Table 6: Bimatoprost and timolol discontinuation across trials

Bimatoprost and timolol study	Annual discontinuation rate
MERCURY-3: a randomized comparison of netarsudil/latanoprost and bimatoprost/timolol in open-angle glaucoma and ocular hypertension[12]	12.26%
Safety of Fixed-Combination Bimatoprost 0.03%/Timolol 0.5% Ophthalmic Solution at 6 Months in Chinese Patients with Open-Angle Glaucoma or Ocular Hypertension[13]	25.66%
The Safety and Efficacy of Bimatoprost/Timolol Fixed Combination: A 1-year Double-masked, Randomized Parallel Comparison to Its Individual Components in Patients With Glaucoma or Ocular Hypertension[14]	12.20%
Latanoprost and timolol combination therapy vs monotherapy: one-year randomized trial[15]	18.84%

While a lifetime time horizon is typically included in submissions to NICE, the nature of the netarsudil-latanoprost and its indication is suitable to justify a short time horizon. The availability of data and link between short- and long-term progression of the disease also suggest a shorter time horizon is more suitable, to avoid unrealistic assumptions and extrapolations. Non-lifetime horizons have been accepted in many appraisals including NICE TA471, TA217, and TA729 for indications (irritable bowel syndrome, Alzheimer's disease, hyperphenylalaninaemia in phenylketonuria).[16,17]

As such, for the base case, the economic model and budget impact model has been adapted to apply a 1-year time horizon. Table 5 shows this to be an underestimation for the median time on treatment for all products, including netarsudil-latanoprost, excluding Brimonidine and timolol. The Company feel it more appropriate to present results with an underestimation for time on treatment than to overestimate the time patients remain on their product – this approach is considered the conservative option.

		Additionally, to reflect costs which are considered when a patient is on active treatment, the cost of surgical treatments (SLT/ trabeculectomy) are removed – as it would be expected that patients take a break from treatment following surgery, a break not accounted for in a condensed time horizon. To demonstrate the limited impact the changes in the time horizon, and subsequent removal of discontinuation have on the positioning of netarsudil-latanoprost in the QALY League tables, scenario analyses have been included presenting results at time horizons of 2 years, 5 years and with the cost of surgeries included. The results remain largely unchanged with netarsudil-latanoprost remaining 8th in the cost per QALY league table, for the 2-year, and 5-year time horizon scenarios, as well as the 1-year with surgery costs included scenario. Inclusion of surgery costs is the least impactful of the three scenarios, increasing total costs and QALYs by £[redacted] and [redacted], respectively. The 2-year time horizon scenario increases costs and QALYs by £[redacted] and [redacted], respectively, while the 5-year time horizon increases costs and QALYs by £[redacted] and [redacted], respectively. Assessment of the removal of discontinuation is not considered meaningful for a time horizon less than lifetime.
3: Company's assumption that those who discontinue treatment have the same intraocular pressure as those who remain	Yes	See response to Issue 2.

<table>
<tr><td>on treatment</td><td></td><td></td></tr>
<tr><td>4: Company's approach to applying health state utility values creates uncertainty</td><td>Yes/No</td><td>
In the original company submission, SF-36 data from the MERCURY 3 trial was mapped to EQ-5D to inform health state utility values in the economic model. The use of the EQ-5D is in line with the NICE reference case,[18] and so the company maintain that this is the correct approach for the appraisal. There is no evidence to suggest that the reference case should be deviated from. However, an issue has been raised by the EAG in that the SF-36 can be used to directly generate utilities by converting it to SF-6D and applying the SF-6D tariff.

In consideration of the critique, the Company have developed health state utility values using the SF-6D to characterise the uncertainty in the health state utility values with the EQ-5D tariff applied. The SF-6D tariff was applied to the SF-36 data of MERCURY-3 using the recognised algorithm, developed by the creators of SF-36 and SF-6D.[19] Then, the SF-6D data was descriptively summarised from MERCURY 3 disaggregated by health state, pooling data from the netarsudil-latanoprost and bimatoprost-timolol treatment arms, to address concerns raised by the EAG regarding use of the EQ-5D rather than SF-6D from the trial SF-36 data.[20] The SF-6D health state utility values were then applied in the economic model as a scenario analysis. The utility values used are detailed in Table 7 below. Comparing the SF-6D utility values with the EQ-5D utility values, it can be seen that the trend of increasing HRQoL with increasing reduction in IOP is maintained. The SF-6D values demonstrate a greater benefit in attaining a threshold of 20% improvement in IOP compared to the EQ-5D, demonstrating that the EQ-5D utility values may be conservative. Regardless, the EQ-5D utility values are maintained by the company in their base case as it is better aligned to the NICE reference case.

Table 7. Health state utility values
<table>
<tr><th>Health state</th><th>EQ-5D utility value (standard error) – reproduced from the company submission</th><th>SF-6D utility value (Standard error) – sensitivity analysis</th></tr>
<tr><td><20% reduction in IOP</td><td>[redacted]</td><td>0.732 (0.01)</td></tr>
<tr><td>20% - 30% reduction in IOP</td><td>[redacted]</td><td>0.751 (0.01)</td></tr>
<tr><td>>30% reduction in IOP</td><td>[redacted]</td><td>0.751 (0.01)</td></tr>
</table>
Abbreviations: IOP – intraocular pressure; SF-6D – Short-Form Six-Dimension Questionnaire

CEM scenario analysis results
</td></tr>
</table>

		The SF-6D health state utility values were applied in the CEM alongside changes made for the updated base case, including changes to the time horizon, discontinuation assumptions, and AE resource use assumptions as detailed in their respective issues. When the SF-6D sensitivity utility analysis was applied in the economic model, netarsudil-latanoprost was associated with a total cost of £[redacted] and a total QALY of [redacted]. Netarsudil-latanoprost was dominated by most comparators except for travoprost-timolol and bimatoprost-timolol. Compared to travoprost-timolol, netarsudil-latanoprost was associated with greater costs and QALYs. Compared to bimatoprost-timolol, netarsudil-latanoprost was associated with lower costs and QALYs. Compared with the updated base case analysis, in this sensitivity analysis, netarsudil-latanoprost was associated with fewer QALYs ([redacted] QALYs when SF-6D is considered, compared to [redacted] in the updated base case where EQ-5D is considered). Similar to the SF-6D sensitivity utility analysis results, netarsudil-latanoprost was dominated by most comparators except for travoprost-timolol. Compared to travoprost-timolol, netarsudil-latanoprost was associated with greater costs and QALYs. Compared to bimatoprost-timolol, netarsudil-latanoprost was associated with lower costs and QALYs.
5: Company's assumption of an average market share of branded and generic comparators within class, prescribed in	No	The Company maintains their existing stance on this topic. The reasoning and supportive evidence to the use of the market share values inclusive of both generic and branded products has been well documented throughout The Company's submission. For reference, please refer to the following sections of previously submitted documents for justification: • Document A, Table 5. • Document B, page 120. • Document B, Table 62. • BIA, page 22. • EAG report response, page 8. • EAG report response, page 13. • Clarification questions, page 64. Throughout the submission documents, it has been communicated that market share data is based on UK sales data from December 2015 to December 2022. These values are based on data, not assumption.

primary care		Market share for products between classes is based on 2022 sales data, with trends from 2015 to 2022 extrapolated at the same trajectory for 2023 to 2028 (to cover the time horizon of the budget impact model). Any use of market share values beyond 5 years are assumed to the last observation carried forwards. It is therefore considered inappropriate to use generic products only, as this would be an unrepresentative approach for the market. Market shares for in class is based on 2022 sales data and applied to all years of the model.
6: Company's assumption of more intensive use of secondary care resources to manage mild and moderate adverse events than would be expected in UK clinical practice	Yes	In line with the concerns raised by the EAG, the Company have adjusted the resource use associated with managing adverse events (AEs) in the economic model by their severity as reported in the MERCURY-3 trial. The resource use of AEs were adjusted so that resource use reflected the severity of the AE. The reported number of AEs by severity in the netarsudil-latanoprost and bimatoprost-timolol arms from the MERCURY-3 trial were firstly used to calculate the percentage of AEs by severity, as shown in Table 27 of the Appendix. AEs of mild severity were subsequently excluded from further resource use calculations as mild AEs were assumed to not require any resource use to manage them. For moderate AEs, it was assumed that the resource use was in line with the EAG's preferred resource use assumptions, as shown in Table 26 of the Appendix. For severe AEs, it was assumed that resource was in line with the original submission, as detailed in Table 58 of Document B, which was reflective of a higher severity AE. The total cost of each AE in the netarsudil-latanoprost and bimatoprost-timolol trial arms was then calculated according to the frequency of events by their severity, as shown in Table 28 of the Appendix. **Comparison with previous base case for AE costs results:** With the updates to the costs of AEs alongside the other base case changes, netarsudil-latanoprost was associated with total costs of £[redacted] and QALYs of [redacted]. When the previous base case assumptions for AE costs were applied in the economic model (i.e., all AEs require the resource level of a severe AE), netarsudil-latanoprost was associated with a total cost of £[redacted] and a total QALY of [redacted], as shown in Table 19 of the Appendix. This demonstrates that the revised approach to the cost of AEs results in fewer costs. This was the case for all comparators too, as the cost of AEs associated with all treatments considered was reduced.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
n/a			

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	*Briefly describe the company's original preferred assumption or analysis*	*Briefly describe the change(s) made in response to the EAR*	*Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.*
Not applicable	Brimonidine-timolol costs per drop were incorrectly calculated due to a typographical error on unit size for the sub-product "COMBIGANEYEDROPS15ML (3*5ml)".	In line with the changes described during the response to the EAG report, the price of brimonidine-timolol has been updated to be based on 15ml per pack as opposed incorrectly reported as 5ml per pack. This change reduces the price per ml from £5.40 to £1.80.	This change reduces the total costs associated with brimonidine-timolol.
2. Economic model structure does not capture disease progression AND 3. Company's assumption that those	Previously The Company submitted a model in which the time horizon was assumed to be representative of a life-time horizon (100 years old minus base line age). Additionally, to represent the movement of	As outlined above – discontinuation has been removed from the model, the time horizon reduced to 1year, and the costs of SLT and trabeculectomy surgeries removed.	Due to the interweaved issues, analysing changes in the ICER solely due to time horizon, discontinuation costs, and removal of surgical costs is not an intuitive presentation of results. Instead, assessing the deviation from The

who discontinue treatment have the same intraocular pressure as those who remain on treatment	patients between treatments due to discontinuation, post-discontinuation costs and clinical data were analysed. Further, as a lifetime model was being presented, cost of SLT and trabeculectomy surgeries were accounted for.		Company's preferred base-case is more meaningful. Increasing the time horizon to either 2years or 5years to assess the impact of assuming time horizon of 1 year, or the removal or surgical costs, whilst keeping all other elements of the model in the preferred updated base case, netarsudil-latanoprost's position in the incremental league table does not change – showing limited impact of these changes. A time horizon of 2 years increases total costs and QALYs for netarsudil-latanoprost by £[redacted] and [redacted], respectively. A time horizon of 5 years increases total costs and QALYs for netarsudil-latanoprost by £[redacted] and [redacted], respectively. The inclusion of surgical costs increases total costs and QALYs for netarsudil-latanoprost by £[redacted] and [redacted], respectively. Assessment of the removal of discontinuation is not considered meaningful for a time horizon less than life-time.
6: Company's assumption of more intensive use of secondary care resources to manage	The total cost per AE occurrence was obtained by multiplying the resource use unit cost by the event frequency as reported in the MERCURY-3	The resource use associated with managing AEs were adjusted by their severity as reported in the MERCURY-3 trial, so that	When the previous base case assumptions for AE costs (all AEs require the resource level of a severe AE) were applied, netarsudil-latanoprost was dominated by most FDC

mild and moderate adverse events than would be expected in UK clinical practice	trial. The cost for each treatment was applied by taking the AE total costs and multiplying by the probability of the AE occurring for that therapy. The AE resource use assumptions were as described in Table 58 of Document B.	resource use would reflect the severity of the AE. Mild AEs were assumed to not require any intervention. Moderate AEs were assumed to require resource use that was In line with the EAG's preferred resource use assumptions. Severe AEs were assumed to require resource use that was in line with the original submission's resource use assumptions. The total cost for each AE was then calculated according to the frequency of events by their severity.	comparators except for travoprost-timolol. Compared to travoprost-timolol, netarsudil-latanoprost was associated with greater costs and QALYs. Netarsudil-latanoprost was associated with an average cost of £[redacted]. Compared with the associated incremental costs and QALYs of other comparators except for travoprost-timolol, netarsudil-latanoprost was dominated. However, the difference in incremental QALYs between an FDC comparator and netarsudil-latanoprost was extremely small with a range between [redacted] (versus travoprost-timolol) and [redacted] (versus brinzolamide-brimonidine, dorzolamide-timolol, latanoprost-timolol, and bimatoprost-timolol). For the updated base case analysis (resource use of AEs aligned with severity), deterministic results showing incremental costs, life years gained (LYG), and QALYs for each FDC comparator versus netarsudil-latanoprost is presented in Table 23 of the Appendix. An incremental analysis showing the total costs, LYG, QALYs, ICER versus baseline, and ICER versus previously shown comparator for each FDC therapy is presented in Table 9 of the Appendix. In the updated base case analysis, netarsudil-latanoprost was dominated by other FDC comparators except for

			travoprost-timolol and bimatoprost-timolol. Compared to travoprost-timolol, netarsudil-latanoprost was associated with greater costs and QALYs. Compared to bimatoprost-timolol, netarsudil-latanoprost was associated with lower costs and QALYs. Netarsudil-latanoprost was associated with an average cost of £[redacted], being more cost-saving than bimatoprost-timolol (£[redacted]). The associated incremental costs and QALYs of netarsudil-latanoprost resulted in it being dominated by brinzolamide-timolol, dorzolamide-timolol, latanoprost-timolol, tafluprost-timolol, brimonidine-timolol, and brinzolamide-brimonidine. The difference in incremental QALYs between an FDC comparator and netarsudil-latanoprost had remained at a relatively small difference when compared with the previous base case analysis to a range between [redacted] (versus travoprost-timolol) and [redacted] (versus tafluprost-timolol and brinzolamide-brimonidine).
Company's base case following technical engagement (or revised base case)	Total QALYs: [redacted]	Total costs: [redacted]	Total QALYs: [redacted] Incremental costs: £[redacted] ICER: [redacted]

Table 8. Deterministic revised base case incremental analysis (incremental results of each comparator vs. netarsudil latanoprost)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs. netarsudil-latanoprost	Net monetary benefit (NMB)
Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
Brinzolamide-timolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Travoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,305	[redacted]
Dorzolamide-timolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Latanoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Tafluprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,416	[redacted]
Brimonidine-timolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Brinzolamide-brimonidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life year gained; NMB – net monetary benefit; QALY – quality-adjusted life year

Table 9. Deterministic revised base case results (incremental results vs. treatment with lowest total costs)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs. incremental QALYs	Net monetary benefit (NMB)
Brinzolamide-timolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
Dorzolamide-timolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

Brinzolamide-brimonidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,063	[redacted]
Latanoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Travoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Brimonidine-timolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Tafluprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life year gained; NMB – net monetary benefit; QALY – quality-adjusted life year

Sensitivity analyses around revised base case

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted using the revised base case to estimate the uncertainties in the key model parameters. This was performed for each parameter simultaneously over multiple iterations. 10,000 iterations were run for the base case analysis to ensure stability in results. Further details of the PSA were as described in Appendix D of the clarification response.

Table 10 shows the mean results of the PSA comparing the FDC with the lowest treatment cost versus all other comparators. Probabilistic costs, LYs, and QALYs were generally consistent with the deterministic results. Netarsudil-latanoprost was associated with a total cost of [redacted] and mean total QALYs of [redacted]. The mean probabilistic results are similar to the base case for all comparators.

The ICEP is presented in

Figure 6, and shows that netarsudil-latanoprost is generally more costly but less effective than some FDC comparators, with mean PSA points displayed in the north-west quadrant. Netarsudil-latanoprost is less costly and less effective than bimatoprost-timolol, and more effective and more costly than travoprost-timolol.

Table 10. PSA incremental results

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Cost per QALY (£)
Brinzolamide-timolol	[redacted]	0.986	[redacted]	[redacted]	-	[redacted]	-
Dorzolamide-timolol	[redacted]	0.986	[redacted]	[redacted]	0.000	[redacted]	Dominated
Brinzolamide-brimonidine	[redacted]	0.986	[redacted]	[redacted]	0.000	[redacted]	50,810
Latanoprost-timolol	[redacted]	0.986	[redacted]	[redacted]	0.000	[redacted]	Dominated
Travoprost-timolol	[redacted]	0.986	[redacted]	[redacted]	0.000	[redacted]	Dominated
Brimonidine-timolol	[redacted]	0.986	[redacted]	[redacted]	0.000	[redacted]	Dominated
Tafluprost-timolol	[redacted]	0.986	[redacted]	[redacted]	0.000	[redacted]	Dominated
Netarsudil-latanoprost	[redacted]	0.986	[redacted]	[redacted]	0.000	[redacted]	Dominated
Bimatoprost-timolol	[redacted]	0.986	[redacted]	[redacted]	0.000	[redacted]	Dominated

Abbreviations: LYG – life years gained; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year

Figure 6. ICEP for netarsudil-latanoprost versus FDC comparators

Abbreviations: FDC – fixed-dose combination; ICEP – incremental cost-effectiveness plane; QALY – quality-adjusted life year

The CEAC is shown in Figure 7 to illustrate the probability of netarsudil-latanoprost being cost-effective compared with comparators at various willingness-to-pay thresholds.

Figure 7. CEAC for netarsudil-latanoprost versus FDC comparators

Abbreviations: CEAC – cost-effectiveness analysis curve; FDC – fixed-dose combination

Deterministic sensitivity analysis

A one-way sensitivity analysis (OWSA) was used to assess the effect of parameter variation on net monetary benefit (NMB). The OWSA was performed using a SE approach. Further details of the OWSA are as described in Appendix D of the clarification response.

A tornado diagram was developed to graphically present the parameters for all variables which have the greatest effect on the NMB, at a willingness-to-pay (WTP) threshold of £30,000 per QALY.

The OWSA was performed for netarsudil-latanoprost compared with each FDC comparator in the model. The results are presented in the subsections below.

Netarsudil-latanoprost versus brinzolamide-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB, for the comparison of netarsudil-latanoprost with brinzolamide-timolol is presented in Figure 8 with tabulated results presented Table 11. The model was most sensitive to the netarsudil-latanoprost cost per cycle.

Figure 8. OWSA tornado diagram for netarsudil-latanoprost versus brinzolamide-timolol: NMB

Abbreviations: IOP – intraocular pressure; NMB – net monetary benefit; OWSA – one-way sensitivity analysis

Table 11. Tabulated OWSA results for netarsudil-latanoprost versus brinzolamide-timolol: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
Netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	[redacted]

Brinzolamide-timolol cost per cycle (£)	[redacted]	[redacted]	[redacted]
Utility: >30% reduction in IOP	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 4+)	[redacted]	[redacted]	[redacted]
Utility: 20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 1)	[redacted]	[redacted]	[redacted]
Brinzolamide-timolol adverse event total disutility (cycle 1)	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 2)	[redacted]	[redacted]	[redacted]
Brinzolamide-timolol adverse event total disutility (cycle 2)	[redacted]	[redacted]	[redacted]
Brinzolamide-timolol adverse event total disutility (cycle 3)	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – intraocular pressure; NMB – net monetary benefit; OWSA – one-way sensitivity analysis

Netarsudil-latanoprost versus dorzolamide-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB, for the comparison of netarsudil-latanoprost with dorzolamide-timolol is presented in Figure 9, with tabulated results presented in Table 12**Error! Reference source not found.**. The model was most sensitive to the netarsudil-latanoprost cost per cycle.

Figure 9. OWSA tornado diagram for netarsudil-latanoprost versus dorzolamide-timolol: NMB

Abbreviations: IOP – intraocular pressure; NMB – net monetary benefit; OWSA – one-way sensitivity analysis

Table 12. Tabulated OWSA results for netarsudil-latanoprost versus dorzolamide-timolol: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
Netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	[redacted]

Dorzolamide-timolol cost per cycle (£)	[redacted]	[redacted]	[redacted]
Utility: >30% reduction in IOP	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 4+)	[redacted]	[redacted]	[redacted]
Utility: 20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 1)	[redacted]	[redacted]	[redacted]
Dorzolamide-timolol adverse event total disutility (cycle 1)	[redacted]	[redacted]	[redacted]
Dorzolamide-timolol adverse event total disutility (cycle 4+)	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 2)	[redacted]	[redacted]	[redacted]
Dorzolamide-timolol adverse event total disutility (cycle 2)	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – intraocular pressure; NMB – net monetary benefit; OWSA – one-way sensitivity analysis

Netarsudil-latanoprost versus latanoprost-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB, for the comparison of netarsudil-latanoprost with latanoprost-timolol is presented in Figure 10, with tabulated results presented in Table 13**Error! Reference source not found.**. The model was most sensitive to netarsudil-latanoprost cost per cycle.

Figure 10. OWSA tornado diagram for netarsudil-latanoprost versus latanoprost-timolol: NMB

Abbreviations: IOP – intraocular pressure; NMB – net monetary benefit; OWSA – one-way sensitivity analysis

Table 13. Tabulated OWSA results for netarsudil-latanoprost versus latanoprost-timolol: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
Netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	[redacted]

Latanoprost-timolol cost per cycle (£)	[redacted]	[redacted]	[redacted]
Latanoprost-timolol adverse event total disutility (cycle 4+)	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 4+)	[redacted]	[redacted]	[redacted]
Utility: >30% reduction in IOP	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 1)	[redacted]	[redacted]	[redacted]
Utility: 20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 2)	[redacted]	[redacted]	[redacted]
Latanoprost-timolol adverse event total disutility (cycle 1)	[redacted]	[redacted]	[redacted]
Latanoprost-timolol adverse event total disutility (cycle 2)	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – intraocular pressure; NMB – net monetary benefit; OWSA – one-way sensitivity analysis

Netarsudil-latanoprost versus tafluprost-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB, for the comparison of netarsudil-latanoprost with tafluprost-timolol is presented in Figure 11,with tabulated results presented in Table 14. The model was most sensitive to tafluprost-timolol cost per cycle.

Figure 11. OWSA tornado diagram for netarsudil-latanoprost versus tafluprost-timolol: NMB

Abbreviations: IOP – intraocular pressure; NMB – net monetary benefit; OWSA – one-way sensitivity analysis

Table 14. Tabulated OWSA results for netarsudil-latanoprost versus tafluprost-timolol: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
Tafluprost-timolol cost per cycle (£)	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	[redacted]

Utility: >30% reduction in IOP	[redacted]	[redacted]	[redacted]
Utility: <20% reduction in IOP	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 4+)	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 1)	[redacted]	[redacted]	[redacted]
Tafluprost-timolol adverse event total disutility (cycle 1)	[redacted]	[redacted]	[redacted]
>30% reduction in IOP total cost	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 2)	[redacted]	[redacted]	[redacted]
<20% reduction in IOP total cost	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – intraocular pressure; NMB – net monetary benefit; OWSA – one-way sensitivity analysis

Netarsudil-latanoprost versus bimatoprost-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB, for the comparison of netarsudil-latanoprost with bimatoprost-timolol is presented in Figure 12, with tabulated results presented in Table 15. The model was most sensitive to bimatoprost-timolol cost per cycle.

Figure 12. OWSA tornado diagram for netarsudil-latanoprost versus bimatoprost-timolol: NMB

Abbreviations: IOP – intraocular pressure; NMB – net monetary benefit; OWSA – one-way sensitivity analysis

Table 15. Tabulated OWSA results for netarsudil-latanoprost versus bimatoprost-timolol: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
Bimatoprost-timolol cost per cycle (£)	[redacted]	[redacted]	[redacted]

Netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	[redacted]
Utility: >30% reduction in IOP	[redacted]	[redacted]	[redacted]
Utility: <20% reduction in IOP	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 4+)	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 1)	[redacted]	[redacted]	[redacted]
Bimatoprost-timolol adverse event total disutility (cycle 1)	[redacted]	[redacted]	[redacted]
Bimatoprost-timolol adverse event total disutility (cycle 4+)	[redacted]	[redacted]	[redacted]
>30% reduction in IOP total cost	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 2)	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – intraocular pressure; NMB – net monetary benefit; OWSA – one-way sensitivity analysis

Netarsudil-latanoprost versus travoprost-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB, for the comparison of netarsudil-latanoprost with travoprost-timolol is presented in Table 16, with tabulated results presented in Figure 13. The model was most sensitive to the utility for the >30% reduction in IOP health state.

Figure 13. OWSA tornado diagram for netarsudil-latanoprost versus travoprost-timolol: NMB

Abbreviations: IOP – intraocular pressure; NMB – net monetary benefit; OWSA – one-way sensitivity analysis

Table 16. Tabulated OWSA results for netarsudil-latanoprost versus travoprost-timolol: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
Utility: >30% reduction in IOP	[redacted]	[redacted]	[redacted]
Utility: 20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]

Netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	[redacted]
Travoprost-timolol cost per cycle (£)	[redacted]	[redacted]	[redacted]
>30% reduction in IOP total cost	[redacted]	[redacted]	[redacted]
Utility: <20% reduction in IOP	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP total cost	[redacted]	[redacted]	[redacted]
Travoprost-timolol adverse event total disutility (cycle 4+)	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 4+)	[redacted]	[redacted]	[redacted]
<20% reduction in IOP total cost	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – intraocular pressure; NMB – net monetary benefit; OWSA – one-way sensitivity analysis

Netarsudil-latanoprost versus brimonidine-timolol

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB, for the comparison of netarsudil-latanoprost with brimonidine-timolol is presented in Figure 14, with tabulated results presented in Table 17. The model was most sensitive to the utility for the >30% reduction in IOP health state.

Figure 14. OWSA tornado diagram for netarsudil-latanoprost versus brimonidine-timolol: NMB

Abbreviations: IOP – intraocular pressure; NMB – net monetary benefit; OWSA – one-way sensitivity analysis

Table 17. Tabulated OWSA results for netarsudil-latanoprost versus brimonidine-timolol: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
Utility: >30% reduction in IOP	[redacted]	[redacted]	[redacted]
Utility: 20% - 30% reduction in IOP	[redacted]	[redacted]	[redacted]

Netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	[redacted]
Brimonidine-timolol cost per cycle (£)	[redacted]	[redacted]	[redacted]
>30% reduction in IOP total cost	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 4+)	[redacted]	[redacted]	[redacted]
20% - 30% reduction in IOP total cost	[redacted]	[redacted]	[redacted]
Utility: <20% reduction in IOP	[redacted]	[redacted]	[redacted]
Brimonidine-timolol adverse event total disutility (cycle 1)	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 1)	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – intraocular pressure; NMB – net monetary benefit; OWSA – one-way sensitivity analysis

Netarsudil-latanoprost versus brinzolamide-brimonidine

A OWSA tornado diagram presenting the top 10 most sensitive parameters to the NMB, for the comparison of netarsudil-latanoprost with brinzolamide-brimonidine is presented in Figure 15, with tabulated results presented in Table 18. The model was most sensitive to netarsudil-latanoprost cost per cycle.

Figure 15. OWSA tornado diagram for netarsudil-latanoprost versus brinzolamide-brimonidine: NMB

Abbreviations: IOP – intraocular pressure; NMB – net monetary benefit; OWSA – one-way sensitivity analysis

Table 18. Tabulated OWSA results for netarsudil-latanoprost versus brinzolamide-brimonidine: NMB

Parameter	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
Netarsudil-latanoprost cost per cycle (£)	[redacted]	[redacted]	[redacted]

Brinzolamide-brimonidine cost per cycle (£)	[redacted]	[redacted]	[redacted]
Utility: >30% reduction in IOP	[redacted]	[redacted]	[redacted]
Utility: <20% reduction in IOP	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 4+)	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 1)	[redacted]	[redacted]	[redacted]
Brinzolamide-brimonidine adverse event total disutility (cycle 1)	[redacted]	[redacted]	[redacted]
>30% reduction in IOP total cost	[redacted]	[redacted]	[redacted]
Netarsudil-latanoprost adverse event total disutility (cycles 2)	[redacted]	[redacted]	[redacted]
<20% reduction in IOP total cost	[redacted]	[redacted]	[redacted]

Abbreviations: IOP – intraocular pressure; NMB – net monetary benefit; OWSA – one-way sensitivity analysis

Scenario analyses

Table 19: Scenario analysis deterministic results (incremental results vs. treatment with lowest total costs)

Scenario	Technologies	Deterministic					
		Total costs (£)	Total QALYs (£)	Incremental costs (£)	Incremental QALYs	ICER (£) versus incremental QALYs	Net monetary benefit (£) versus lowest total cost
5-year time horizon	Brinzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
	Dorzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brinzolamide and brimonidine	[redacted]	[redacted]	[redacted]	[redacted]	77,487	[redacted]
	Latanoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Travoprost and Timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brimonidine and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Tafluprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Bimatoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
2-year time horizon	Brinzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
	Dorzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brinzolamide and brimonidine	[redacted]	[redacted]	[redacted]	[redacted]	63,882	[redacted]
	Latanoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Travoprost and Timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brimonidine and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Tafluprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Bimatoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brinzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]

SLT and trabeculectomy concomitant treatment costs included	Dorzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brinzolamide and brimonidine	[redacted]	[redacted]	[redacted]	[redacted]	49,767	[redacted]
	Latanoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brimonidine and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Travoprost and Timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Tafluprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Bimatoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
All TEAEs modelled as severe	Brinzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
	Brinzolamide and brimonidine	[redacted]	[redacted]	[redacted]	[redacted]	37,482	[redacted]
	Dorzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brimonidine and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Latanoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Bimatoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Travoprost and Timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Tafluprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
NMA sensitivity analysis – random effects analysis	Brinzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
	Dorzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brinzolamide and brimonidine	[redacted]	[redacted]	[redacted]	[redacted]	18,979	[redacted]
	Latanoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Travoprost and Timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brimonidine and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Tafluprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

	Bimatoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
NMA sensitivity analysis – fixed effect analysis	Brinzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
	Dorzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brinzolamide and brimonidine	[redacted]	[redacted]	[redacted]	[redacted]	21,049	[redacted]
	Latanoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Travoprost and Timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brimonidine and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Tafluprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Bimatoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
SF-6D HSUVs	Brinzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
	Dorzolamide and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brinzolamide and brimonidine	[redacted]	[redacted]	[redacted]	[redacted]	46,992	[redacted]
	Latanoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Travoprost and Timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brimonidine and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Tafluprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Bimatoprost and timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

Abbreviations: HSUVs – health state utility values; ICER – incremental cost-effectiveness ratio; NMA – network meta-analysis; QALY – quality adjusted life year; SF-6D – short-form six-dimension; SLT – selective laser trabeculoplasty; TEAE – treatment-emergent adverse event

Appendix

Issue 1

Table 20: Comparison of study design of the additional studies considered for the NMA sensitivity analysis

Trial	Population	Phase	Study design	Geography
ROCKET 1[5]	Patients with OAG or OHT	Phase 3	Double-masked, randomised, multicentre, active-controlled, parallel group study	US
ROCKET 2[3]	Patients with OAG or OHT	Phase 3	Double-masked, randomised, multicentre, active-controlled, parallel group study	US
ROCKET 4[4]	Patients with OAG or OHT	Phase 3	Double-masked, randomised, non-inferiority study	US (50 investigational sites)
Brogliatti *et al*. (2000)[1]	Patients with POAG	NR	NR	Italy
Fechtner *et al*. (2004)[2] (Study 1)	Patients with OAG or OHT	NR	Parallel group, [2]randomised, observer-masked and patient-masked study	US (20 investigational sites)

Abbreviations: NMA – network meta-analysis; NR – not reported; OAG – open angle glaucoma; OHT – ocular hypertension; POAG – primary open angle glaucoma; US – United States

Table 21: Comparison of study design of the additional studies considered for the NMA sensitivity analysis (continued)

Trial	Intervention(s)	Randomisation	Randomisation method	Blinding	Follow-up duration
ROCKET 1[5]	Treatment arm 1: Netarsudil **0.02%** Treatment arm 2: Timolol 0.5%	Patients were randomised to receive netarsudil 0.02% or timolol 0.5% in both eyes	Computer generated allocation schedule	Double-blinded	3 months
ROCKET 2[3]	Treatment arm 1: Netarsudil 0.02% Treatment arm 2: Timolol 0.5%	Patients were randomised to receive netarsudil 0.02% or timolol 0.5% in both eyes	Computer generated allocation schedule	Double-blinded	12 months
ROCKET 4[4]	Treatment arm 1: **Netarsudil 0.02%** Treatment arm 2: Timolol 0.5%	Patients were randomised 1:1 to receive netarsudil 0.02% or timolol 0.5%. Randomisation was stratified by study site and maximum baseline IOP (<25 mmHg vs ≥25 mmHg)	Computer generated allocation schedule	Double-blinded	6 months
Brogliatti *et al*. (2000)[1]	Treatment arm 1: Dorzolamide **2%/timolol 0.5%** Treatment arm 2: Timolol 0.5%	NR	NR	NR	30 days

Fechtner *et al*. (2004)[2]	Treatment arm 1: **Dorzolamide 2% /timolol 0.5%** Treatment arm 2: Latanoprost 0.005%	Patients were randomised to receive dorzolamide 2%/timolol 0.5% or latanoprost 0.005%	Computer generated allocation schedule	Observer-blinded and patient-blinded	3 months

Abbreviations: IOP – intraocular pressure; mmHg – millimetres of Mercury; NMA – network meta-analysis; NR – not reported

Table 22: Comparison of baseline characteristics in the additional studies considered for the NMA sensitivity analysis

Baseline characteristic	Trial			
	MERCURY 1[7]	MERCURY 2[6]	Fechtner *et al*. (2004)[2]	
Treatment arm (sample size)	Netarsudil (244)	Netarsudil (255)	Dorzolamide-timolol (128)	Latanoprost (128)
Mean age (years) (SD)	64.6 (10.97)	64.5 (10.58)	63.1 (11.9)	62.6 (12.7)
IOP at screening – study eye (mmHg), mean (SD)	19.5 (4.1130)	20.5 (NR)	NR	NR
Mean diurnal IOP (mmHg) at baseline, mean (SD)	23.6 (NR)	23.6 (NR)	26.1 (4.2)	25.6 (3.9)
Visual field mean deviation (dB), mean ± SD	Study eye: -2.38 dB; fellow eye: -2.12 dB	Study eye -2.36 dB; fellow eye -2.50 dB	NR	NR
Corneal thickness (µm), mean ± SD	NR	NR	NR	NR

Family history of glaucoma	NR	NR	NR	NR
Cup to disc ratio, mean ± SD	NR	NR	NR	NR
Disc haemorrhages	NR	NR	NR	NR
Baseline visual field indices	NR	NR	NR	NR
Retinal nerve fibre layer	NR	NR	NR	NR
Corneal hysteresis	NR	NR	NR	NR
Previous treatment[a]	Prior hypotensive therapy Combination therapy: 30 (12.3) PGA (monotherapy): 144 (59.0) Other **(monotherapy): 12 (4.9)** No prior therapy: 58 (23.8) Prior hypotensive therapy Prior PGA therapy: **171 (70.1)** No prior PGA therapy: 73 (29.9)	Prior hypotensive therapy**.** Combination therapy: **35 (13.7)** PGA **(monotherapy): 112 (43.9)** Other (monotherapy): **14 (5.5)** No prior therapy: **94 (36.9)** Prior hypotensive therapy Prior **PGA therapy: 140 (54.9)** No prior PGA therapy: 115 (45.1)	IOP therapy prior to washout % **timolol**: **53** % **dorzolamide**: **9** % **latanoprost**: **15** % other: 40	IOP **therapy prior to washout** % **timolol**: **42** % **dorzolamide**: **14** % **latanoprost**: **12** % other: 33

Abbreviations: dB – decibels; IOP – intraocular pressure; mmHG – millimetres of Mercury; NMA – network meta-analysis; NR – not reported; PGA – prostaglandin analogue; SD – standard deviation; µm – micrometres
[a]Previous treatment was not deemed to be a key prognostic variable or treatment effect modifier; previous treatment is included in baseline characteristics comparison to assess the implications of varying study eligibility criteria between the network.

Table 23: Extracted and derived data from Rigollet *et al*. (2011) for the NMA[21]

Treatment arm	IOP at baseline (mmHg)	Difference in IOP from baseline at month 3 (mmHg)		Derived mean IOP at month 3 (mmHg)*
		Mean	SD	
Latanoprost-timolol	27.60	-8.31	4.57	19.29
Travoprost-timolol	26.40	-6.50	3.66	19.90
Bimatoprost-timolol	28.00	-8.69	4.24	19.31

Abbreviations: IOP – intraocular pressure; mmHG – millimetres of Mercury; NMA – network meta-analysis; SD – standard deviation
*Mean IOP at month 3 was derived by subtracting the absolute mean difference in IOP from baseline at month 3 from the baseline IOP for each comparator.

Table 24. Publications and data used for the NMA sensitivity analysis

Study	Treatment arm	Timepoint	Time	Mean IOP* (mmHg)	SE of mean IOP*	Data manipulation required
Rigollet *et al*. (2011)[21]	Latanoprost-timolol	Baseline	NR	27.60	3.25	• SD estimated as the average of SDs at baseline reported across the remaining studies at baseline
		Month 3	NR	19.29	3.43	• Mean IOP estimated using baseline IOP and difference in IOP from baseline** • SD estimated as the average of SDs at baseline reported across the remaining studies at month 3
	Travoprost-timolol	Baseline	NR	26.40	3.25	• SD estimated as the average of SDs at baseline reported across the remaining studies at baseline

		Month 3	NR	19.90	3.43	• Mean IOP estimated using baseline IOP and difference in IOP from baseline** • SD estimated as the average of SDs at baseline reported across the remaining studies at month 3
	Bimatoprost-timolol	Baseline	NR	28.00	3.25	• SD estimated as the average of SDs at baseline reported across the remaining studies at baseline
		Month 3	NR	19.31	3.43	• Mean IOP estimated using baseline IOP and difference in IOP from baseline** • SD estimated as the average of SDs at baseline reported across the remaining studies at month 3
MERCURY 1[7]	Netarsudil-latanoprost	Baseline	8AM	24.84	3.32	-
			10AM	23.72	3.59	-
			4PM	22.59	3.61	-
			Diurnal mean	23.72	3.51	• SD estimated using the average SD formula, based on the 8AM, 10AM and 4PM timepoint SDs
		Month 3	8AM	16.37	3.38	-
			10AM	15.41	3.04	-
			4PM	15.49	3.13	-
			Diurnal mean	15.76	3.19	• SD estimated using the average SD formula, based on the 8AM, 10AM and 4PM timepoint SDs
	Netarsudil	Baseline	8AM	24.81	3.335	-
			10AM	23.45	3.51	-
			4PM	22.63	3.674	-

			Diurnal mean	23.63	3.51	• SD estimated using the average SD formula, based on the 8AM, 10AM and 4PM timepoint SDs
		Month 3	8AM	19.04	4.537	-
			10AM	17.96	4.262	-
			4PM	17.3	3.769	-
			Diurnal mean	18.10	4.20	• SD estimated using the average SD formula, based on the 8AM, 10AM and 4PM timepoint SDs
	Latanoprost	Baseline	8AM	24.59	2.91	-
			10AM	23.4	3.39	-
			4PM	22.43	3.37	-
			Diurnal mean	23.48	3.23	• SD estimated using the average SD formula, based on the 8AM, 10AM and 4PM timepoint SDs
		Month 3	8AM	17.53	3.28	-
			10AM	16.88	3.14	-
			4PM	16.67	3.12	-
			Diurnal mean	17.03	3.18	• SD estimated using the average SD formula, based on the 8AM, 10AM and 4PM timepoint SDs
MERCURY 2[6]	Netarsudil-latanoprost	Baseline	8AM	24.69	3.42	-
			10AM	23.33	3.4	-
			4PM	22.37	3.49	-
			Diurnal mean	23.46	3.44	• SD estimated using the average SD formula, based on the 8AM, 10AM and 4PM timepoint SDs
		Month 3	8AM	16.45	3.57	-

			10AM	15.58	3.31	-
			4PM	15.52	3.21	-
			Diurnal mean	15.8500	3.37	• SD estimated using the average SD formula, based on the 8AM, 10AM and 4PM timepoint SDs
	Netarsudil	Baseline	8AM	24.66	3.15	-
			10AM	23.4	3.54	-
			4PM	22.76	3.56	-
			Diurnal mean	23.61	3.42	• SD estimated using the average SD formula, based on the 8AM, 10AM and 4PM timepoint SDs
		Month 3	8AM	19.72	4.42	-
			10AM	18.3	3.85	-
			4PM	17.94	3.63	-
			Diurnal mean	18.65	3.98	• SD estimated using the average SD formula, based on the 8AM, 10AM and 4PM timepoint SDs
	Latanoprost	Baseline	8AM	24.75	3.24	-
			10AM	23.23	3.34	-
			4PM	22.59	3.45	-
			Diurnal mean	23.52	3.34	• SD estimated using the average SD formula, based on the 8AM, 10AM and 4PM timepoint SDs
		Month 3	8AM	17.98	3.4	-
			10AM	17.48	3.37	-
			4PM	17.14	3.04	-

			Diurnal mean	17.53	3.27	• SD estimated using the average SD formula, based on the 8AM, 10AM and 4PM timepoint SDs
MERCURY-3[20]	Netarsudil-latanoprost	Baseline	8AM	-	-	-
			10AM	-	-	-
			4PM	-	-	-
			Diurnal mean	25.10	3.40	-
		Month 3	8AM	16.00	2.90	-
			10AM	15.70	3.10	-
			4PM	15.30	2.80	-
			Diurnal mean	15.67	2.67	-
	Bimatoprost-timolol	Baseline	8AM	-	-	-
			10AM	-	-	-
			4PM	-	-	-
			Diurnal mean	24.80	3.30	-
		Month 3	8AM	15.26	2.70	-
			10AM	15.20	2.70	-
			4PM	15.00	2.80	-
			Diurnal mean	15.15	2.56	-
DuBiner *et al*. (2001)[10]	Brimonidine	Baseline	Diurnal mean	24.50	2.20	-
		Month 3	Diurnal mean	17.70	3.60	-

	Latanoprost	Baseline	Diurnal mean	24.10	1.90	-
		Month 3	Diurnal mean	17.60	3.90	-
Katz *et al*. (2013)[22]	Brinzolamide-brimonidine	Baseline	8AM	26.90	2.60	-
			10AM	25.30	2.80	-
			3PM	23.70	3.00	-
			5PM	23.20	3.10	-
			Diurnal mean	24.78	2.88	• Diurnal mean IOP estimated as the average of IOP values at 8AM, 10AM, 3PM and 5PM timepoints • SD estimated using the average SD formula, based on the 8AM, 10AM, 3PM and 5PM timepoint SDs
		Month 3	8AM	19.80	4.20	-
			10AM	16.50	3.60	-
			3PM	18.00	3.70	-
			5PM	16.30	3.70	-
			Diurnal mean	17.65	3.81	• Diurnal mean IOP estimated as the average of IOP values at 8AM, 10AM, 3PM and 5PM timepoints • SD estimated using the average SD formula, based on the 8AM, 10AM, 3PM and 5PM timepoint SDs
	Brinzolamide	Baseline	8AM	27.10	2.60	-
			10AM	25.40	2.70	-
			3PM	23.80	3.20	-
			5PM	23.60	3.40	-

			Diurnal mean	24.98	2.99	• Diurnal mean IOP estimated as the average of IOP values at 8AM, 10AM, 3PM and 5PM timepoints • SD estimated using the average SD formula, based on the 8AM, 10AM, 3PM and 5PM timepoint SDs
		Month 3	8AM	20.90	4.20	-
			10AM	19.70	4.00	-
			3PM	19.70	3.70	-
			5PM	19.30	3.70	-
			Diurnal mean	19.90	3.91	• Diurnal mean IOP estimated as the average of IOP values at 8AM, 10AM, 3PM and 5PM timepoints • SD estimated using the average SD formula, based on the 8AM, 10AM, 3PM and 5PM timepoint SDs
	Brimonidine	Baseline	8AM	27.00	2.60	-
			10AM	25.40	2.80	-
			3PM	24.00	3.30	-
			5PM	23.70	3.30	-
			Diurnal mean	25.03	3.02	• Diurnal mean IOP estimated as the average of IOP values at 8AM, 10AM, 3PM and 5PM timepoints • SD estimated using the average SD formula, based on the 8AM, 10AM, 3PM and 5PM timepoint SDs
		Month 3	8AM	22.50	4.40	-
			10AM	18.90	3.70	-
			3PM	20.50	3.80	-

			5PM	17.90	3.30	-
			Diurnal mean	19.95	3.82	• Diurnal mean IOP estimated as the average of IOP values at 8AM, 10AM, 3PM and 5PM timepoints • SD estimated using the average SD formula, based on the 8AM, 10AM, 3PM and 5PM timepoint SDs
Whitson *et al*. (2013)[23]	Brinzolamide-brimonidine	Baseline	8AM	27.20	2.80	-
			10AM	25.80	3.10	-
			3PM	24.40	3.70	-
			5PM	24.10	3.70	-
			Diurnal mean	25.38	3.35	• Diurnal mean IOP estimated as the average of IOP values at 8AM, 10AM, 3PM and 5PM timepoints • SD estimated using the average SD formula, based on the 8AM, 10AM, 3PM and 5PM timepoint SDs
		Month 3	8AM	20.50	3.90	-
			10AM	17.50	3.80	-
			3PM	19.00	3.80	-
			5PM	16.70	3.90	-
			Diurnal mean	18.43	3.85	• Diurnal mean IOP estimated as the average of IOP values at 8AM, 10AM, 3PM and 5PM timepoints • SD estimated using the average SD formula, based on the 8AM, 10AM, 3PM and 5PM timepoint SDs
	Brinzolamide	Baseline	8AM	27.20	2.70	-
			10AM	26.00	3.20	-

			3PM	24.40	3.60	-
			5PM	24.20	3.90	-
			Diurnal mean	25.45	3.38	• Diurnal mean IOP estimated as the average of IOP values at 8AM, 10AM, 3PM and 5PM timepoints • SD estimated using the average SD formula, based on the 8AM, 10AM, 3PM and 5PM timepoint SDs
		Month 3	8AM	21.40	4.20	-
			10AM	20.20	3.80	-
			3PM	20.10	4.00	-
			5PM	19.80	3.90	-
			Diurnal mean	20.38	3.98	• Diurnal mean IOP estimated as the average of IOP values at 8AM, 10AM, 3PM and 5PM timepoints • SD estimated using the average SD formula, based on the 8AM, 10AM, 3PM and 5PM timepoint SDs
	Brimonidine	Baseline	8AM	27.30	2.70	-
			10AM	25.80	3.00	-
			3PM	24.00	3.40	-
			5PM	23.70	3.60	-
			Diurnal mean	25.20	3.19	• Diurnal mean IOP estimated as the average of IOP values at 8AM, 10AM, 3PM and 5PM timepoints • SD estimated using the average SD formula, based on the 8AM, 10AM, 3PM and 5PM timepoint SDs
		Month 3	8AM	22.50	4.10	-

			10AM	19.00	3.70	-
			3PM	20.70	4.20	-
			5PM	18.00	4.20	-
			Diurnal mean	20.05	4.06	• Diurnal mean IOP estimated as the average of IOP values at 8AM, 10AM, 3PM and 5PM timepoints • SD estimated using the average SD formula, based on the 8AM, 10AM, 3PM and 5PM timepoint SDs
Kozobolis *et al*. (2017)[8]	Dorzolamide-timolol	Baseline	9AM	28.00	2.40	-
			4PM	28.20	2.50	-
			Diurnal mean	28.10	2.45	• Diurnal mean IOP estimated as the average of IOP values at 9AM and 4PM timepoints • SD estimated using the average SD formula, based on the 9AM and 4PM timepoint SDs
		Month 3	9AM	21.00	3.00	-
			4PM	19.60	2.10	-
			Diurnal mean	20.30	2.59	• Diurnal mean IOP estimated as the average of IOP values at 9AM and 4PM timepoints • SD estimated using the average SD formula, based on the 9AM and 4PM timepoint SDs
	Brinzolamide-brimonidine	Baseline	9AM	28.60	1.80	-
			4PM	28.40	2.00	-
			Diurnal mean	28.50	1.90	• Diurnal mean IOP estimated as the average of IOP values at 9AM and 4PM timepoints • SD estimated using the average SD formula, based on the 9AM and 4PM timepoint SDs
		Month 3	9AM	20.20	1.80	-

			4PM	20.50	1.60	-
			Diurnal mean	20.35	1.70	• Diurnal mean IOP estimated as the average of IOP values at 9AM and 4PM timepoints • SD estimated using the average SD formula, based on the 9AM and 4PM timepoint SDs
Nixon *et al*. (2009)[11]	Dorzolamide-timolol	Baseline	Diurnal mean	23.60	4.50	-
		Month 3	Diurnal mean	17.20	3.20	-
	Brimonidine-timolol	Baseline	Diurnal mean	23.00	4.40	-
		Month 3	Diurnal mean	15.60	3.80	-
Fechtner *et al*. (2004)[2]	Dorzolamide-timolol	Baseline	Diurnal mean	26.10	4.20	-
		Month 3	Diurnal mean	18.90	3.43	• SD estimated as the average of SDs at baseline reported across the remaining studies at month 3
	Latanoprost	Baseline	Diurnal mean	25.60	3.90	-
		Month 3	Diurnal mean	18.40	3.43	• SD estimated as the average of SDs at baseline reported across the remaining studies at month 3

Abbreviations: IOP – intraocular pressure; SD – standard deviation
*Cells filled grey indicate instances where the data value for the NMA has been estimated
**The raw data from the Rigollet et al. (2011) study is presented in Table 20.

Table 25. Data input coding for NMA analysis

Study	Treatment arm coding*	Treatment arm	Mean IOP at baseline (y1_b)	Mean IOP at Month 3 (y1_p)	Standard error at baseline (se1_b)	Standard error at Month 3 (se1_p)

Rigollet *et al.* (2011)	t1	Bimatoprost-timolol (n=42)	28.00	19.31	3.25	3.43
	t2	Latanoprost-timolol (n=42)	27.60	19.29	3.25	3.43
	t3	Travoprost-timolol (n=44)	26.40	19.90	3.25	3.43
MERCURY 1	t4	Netarsudil-latanoprost (n=238)	23.72	15.76	3.51	3.19
	t5	Latanoprost (n=236)	23.48	17.03	3.23	3.18
	t6	Netarsudil (n=244)	23.63	18.10	3.51	4.20
MERCURY 2	t4	Netarsudil-latanoprost (n=245)	23.46	15.85	3.44	3.37
	t5	Latanoprost (n=250)	23.52	17.53	3.34	3.27
	t6	Netarsudil (n=255)	23.61	18.65	3.42	3.98
MERCURY 3	t1	Bimatoprost-timolol (n=212)	24.80	15.15	3.30	2.60
	t4	Netarsudil-latanoprost (n=218)	25.1	15.67	3.40	2.70
DuBiner *et al.* (2001)	t5	Latanoprost (n=61)	24.10	17.60	1.90	3.90
	t7	Brimonidine (n=64)	24.50	17.70	2.20	3.60
Katz *et al.* (2013)	t7	Brimonidine (n=216)	25.03	19.95	3.02	3.82
	t8	Brinzolamide-brimonidine (n=209)	24.78	17.65	2.88	3.81
	t9	Brinzolamide (n=224)	24.98	19.90	2.99	3.91

Whitson *et al.* (2013)	t7	Brimonidine (n=232)	25.20	20.05	3.19	4.06
	t8	Brinzolamide-brimonidine (n=218)	25.38	18.43	3.35	3.85
	t9	Brinzolamide (n=229)	25.45	20.38	3.38	3.98
Kozobolis *et al.* (2017)	t8	Brinzolamide-brimonidine (n=22)	28.50	20.35	1.90	1.70
	t10	Dorzolamide-timolol (n=22)	28.10	20.30	2.45	2.59
Nixon *et al.* (2009)	t10	Dorzolamide-timolol (n=89)	23.60	17.20	4.50	3.20
	t11	Brimonidine-timolol (n=91)	23.00	15.60	4.40	3.80
Fehctner *et al.* (2004)	t5	Latanoprost (n=128)	25.60	18.40	3.90	3.43
	t10	Dorzolamide-timolol (n=128)	26.10	18.90	4.20	3.43

*For each study, the corresponding treatment arm coding was used to define the coding for mean IOP at baseline and Month 3, and standard error at baseline and Month 3. For example, bimatoprost-timolol was coded as t1, thus the corresponding mean IOP at baseline was coded as y1_b, mean IOP at Month 3 as y1_p, standard error at baseline as se1_b, and standard error at Month 3 as se1_p.

Issue 6

Table 26: Revised assumptions for AE of moderate severity resource use

Adverse event	Resource use item	Frequency of resource use	Cost per item (£)	Total cost per item
Conjunctival hyperaemia	Ophthalmology appointment	0	141.97	0
Cornea verticllate	Ophthalmology appointment	0	141.97	0
Conjunctival haemorrhage	Ophthalmology appointment	0.5	141.97	70.99

Eye pruritis	Ophthalmology appointment	0.5	141.97	70.99
	Dermatology appointment	0	152.30	0
Punctuate keratitis	Ophthalmology appointment	0.5	141.97	70.99
Conjunctivitis allergic	Ophthalmology appointment	1	141.97	141.97
Abnormal vision	Ophthalmology appointment	1	141.97	141.97
Blurred vision	Ophthalmology appointment	1	141.97	141.97
Change of eyelashes	Nil	0	0	0
Conjunctival blanching	Nil	0	0	0
Dry eye	Hypromellose eye drops 1-2 drops 3 times daily as needed	0	0.69	0
Eye allergy	Ophthalmology appointment	1	141.97	141.97
Eye irritation	Hypromellose eye drops 1-2 drops 3 times daily as needed	0	0.69	0
Eye pain	Ophthalmology appointment	1	141.97	141.97
Eyelash discolouration	Nil	0	0	0
Foreign body sensation in eye	Ophthalmology appointment	1	141.97	141.97
Ocular discomfort	Ophthalmology appointment	0.5	141.97	141.97
Ocular hyperaemia	Nil	0	0	0
Photophobia	Ophthalmology appointment	0.5	141.97	70.99
Visual disturbance	Ophthalmology appointment	0.5	141.97	70.99

Abbrevations: AE – adverse event

Table 27: Reported percentage of AE by severity

	Netarsudil-latanoprost percentage of AE by severity			Bimatoprost-timolol percentage of AE by severity		
Adverse event	Mild	Moderate	Severe	Mild	Moderate	Severity
Conjunctival hyperaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cornea verticllate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctival haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye pruritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Punctuate keratitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctivitis allergic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abnormal vision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blurred vision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change of eyelashes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctival blanching	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye allergy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye irritation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eyelash discolouration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Foreign body sensation in eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocular discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocular hyperaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Photophobia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual disturbance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 28: AE cost calculations

Adverse event	Resource use item	Weighted proportion of moderate AEs	Weighted proportion of severe AEs	Total cost per AE occurrence (£)
Conjunctival hyperaemia	Ophthalmology appointment	0.79	0.21	44.28
Cornea verticllate	Ophthalmology appointment	1.00	0.00	0.00
Conjunctival haemorrhage	Ophthalmology appointment	1.00	0.00	70.99
Eye pruritis	Ophthalmology appointment	1.00	0.00	70.99
	Dermatology appointment	1.00	0.00	
Punctuate keratitis	Ophthalmology appointment	0.89	0.00	70.99
Conjunctivitis allergic	Ophthalmology appointment	0.00	0.00	158.05
Abnormal vision	Ophthalmology appointment	0.00	0.00	0.00
Blurred vision	Ophthalmology appointment	0.00	0.00	0.00
Change of eyelashes	Nil	0.00	0.00	0.00
Conjunctival blanching	Nil	0.00	0.00	0.00
Dry eye	Hypromellose eye drops 1-2 drops 3 times daily as needed	1.00	0.19	0.00
Eye allergy	Ophthalmology appointment	0.00	1.00	283.95
Eye irritation	Hypromellose eye drops 1-2 drops 3 times daily as needed	0.66	0.34	0.23
Eye pain	Ophthalmology appointment	0.00	1.00	283.95
Eyelash discolouration	Nil	0.00	0.00	0.00
Foreign body sensation in eye	Ophthalmology appointment	1.00	0.00	141.97
Ocular discomfort	Ophthalmology appointment	1.00	0.00	70.99
Ocular hyperaemia	Nil	0.67	0.33	0.00

Photophobia	Ophthalmology appointment	0.00	0.00	0.00
Visual disturbance	Ophthalmology appointment	0.00	0.00	0.00

Abbreviations: AE – adverse event

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Netarsudil-latanoprost for previously treated open-angle glaucoma or ocular hypertension [ID1363]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Monday 22 January 2024**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	1. The Royal College of Ophthalmologists 2. President of UK and Eire Glaucoma Society (UKEGS)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**1. RCOphth - checking with finance team - TBC** **2. UKEGS Congress gets sponsorship from Santen**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1: Non-systematic inclusion of monotherapy trials the network meta-analysis	No	Agree with the EAG there is a need to include all monotherapies in the NMA to prevent bias
2: Economic model structure does not capture disease progression	No	The model provided by the company does not adequately study the long term costs and QALY of IOP changes, it only looks at the short term changes. There are several published economic models listed in the EAG report Table 10 that could be used to construct an appropriate economic model
3: Company's assumption that those who discontinue treatment have the same intraocular pressure as those who remain on treatment	No	This is an incorrect assumption
4: Company's approach to applying health state utility values creates uncertainty	No	Agree, the company's approach does not take into account an important fact, thst of disease progression. This results in over estimation of the long term QALYs
5: Company's assumption of an average market share of branded	No	There is a over estimatation of the branded market in the UK, therefore cost to the NHS. This results in bias in the cost effectiveness of netarsudil-latanoprost

and generic comparators within class, prescribed in primary care		
6: Company's assumption of more intensive use of secondary care resources to manage mild and moderate adverse events than would be expected in UK clinical practice	No	There is an overestimation of the resources that would be used in clinical practice in the UK. Therefore there is a bias in the cost-effectiveness in treatments with higher adverse effects

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Netarsudil-latanoprost for previously treated open-angle glaucoma or ocular hypertension [ID1363]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Friday 26 January 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

NICE National Institute for Health and Care Excellence

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

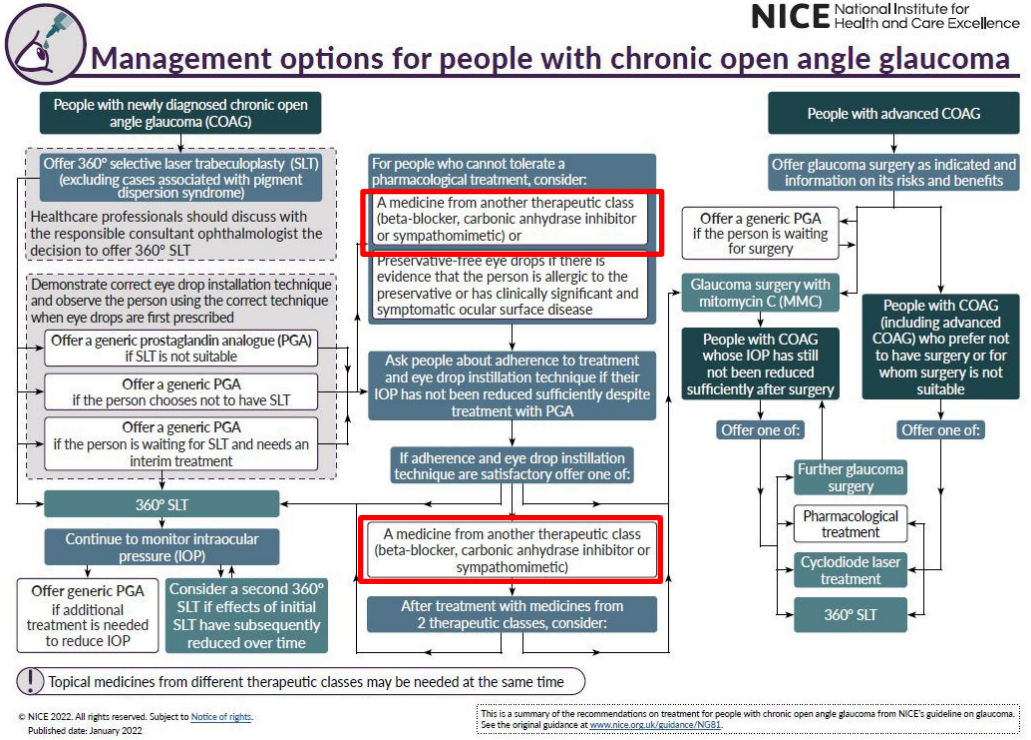
Part 1: Treating open-angle glaucoma or ocular hypertension and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Neeru Vallabh
2. Name of organisation	Liverpool University Hospital Foundation Trust/ University of Liverpool
3. Job title or position	Glaucoma consultant, Clinical Senior Lecturer
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with open-angle glaucoma or ocular hypertension? ☒ A specialist in the clinical evidence base for open-angle glaucoma or ocular hypertension or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☒ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil

8. What is the main aim of treatment for open-angle glaucoma or ocular hypertension? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The ideal therapeutic approach would: a) Prevent progressive retinal ganglion cell loss and protect against optic nerve changes that lead to sight loss. b) Reverse observed changes in retinal ganglion cells and the optic nerve, thereby restoring vision. However, as of now, there is no therapy available to meet these ideal criteria, and ongoing research is being conducted in this field. Currently, the only modifiable risk factor for glaucoma is the reduction of intraocular pressure. Therefore, the primary aim of treatment and the optimal therapy is to lower intraocular pressure. This approach can help prevent the progression of ocular hypertension to open-angle glaucoma or, in the case of open-angle glaucoma, aim to halt or reduce the rate of visual loss.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	In terms of intraocular pressure, this can vary among individual patients, but a target pressure reduction of 20-30% is typically considered a clinically significant response. This assessment is based on several landmark studies, including OHTS, EMGT, CIGTS, and AGIS. Other clinically significant responses encompass stability or improvement in visual fields, stabilisation of optic nerve head changes, and stabilisation of the decline in retinal nerve fibre layer thickness. It is important to note that there is no group consensus on quantifiable parameters in this regard.
10. In your view, is there an unmet need for patients and healthcare professionals in open-angle glaucoma or ocular hypertension?	There is a growing demand for a therapy that not only aids in pressure reduction but also offers neuroprotection. Moreover, there is a necessity for a treatment that can reverse retinal ganglion cell loss. Additionally, there is a call for a therapy capable of restoring the health of the trabecular meshwork, thus addressing the observed increase in pressure associated with aging
11. How is open-angle glaucoma or ocular hypertension currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	The management of ocular hypertension and primary open-angle glaucoma (POAG) involves the use of the following techniques:

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	- Topical medications (Eye drops) - Selective laser trabeculoplasty - Surgery, for example, trabeculectomy Guidance for this treatment is outlined in NICE guidelines NG81: Glaucoma Diagnosis and Management, which is based on clinical expertise and landmark glaucoma studies (https://www.nice.org.uk/guidance/ng81). These guidelines are well-crafted and recognise the diversity in practices, offering various options within the treatment and management pathway. This includes choices such as the selection of which type of second-line drop therapy and the follow-up interval for patient assessments. The technology could provide an alternative therapeutic option for patients after the initiation of primary therapy, as indicated in the highlighted section in red.



12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	If approved, ROCK inhibitors will be prescribed to patients when initial prostaglandin analogue therapy or selective laser trabeculoplasty (SLT) has failed to adequately lower intraocular pressure, serving as a second, third, or fourth-line therapy. Similar to the current clinical practice, the prescription will be based on clinician preference. Presently, clinicians in secondary care or specialist clinics initiate the prescription during consultations, and afterward, general practitioners continue to prescribe it. The pricing may vary compared to alternative options. No additional training is required, as the administration would follow the same procedure as the current topical drop therapy

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The proposed technology has demonstrated, in laboratory studies, the ability to reverse changes that may lead to increased intraocular pressure and optic nerve damage. This involves: 1) Reducing the contraction of the trabecular meshwork and the deposition of extracellular matrix, which contributes to elevated pressure. 2) Adjusting vascular smooth muscle to enhance retinal blood flow and reduce retinal ganglion cell death. These mechanisms present innovative ways to prevent glaucoma progression and reduce the pressure by preventing and potentially reversing the biological changes seen in glaucomatous patients, as demonstrated by laboratory studies. However no studies utilising Rho kinase inhibitors have reported quantifiable data on glaucoma progression, such as visual field defects or neuroretinal rim thinning. The impact of this technology on increasing sight years and improving quality of life will be performed subsequently and would need to be determined through longer-term studies
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Primary open-angle glaucoma (POAG) and ocular hypertension (OHT) are the ideal phenotypes for this treatment and has been the treated group in the primary phase III studies. It would not be appropriate for other forms of glaucoma, such as angle closure, secondary glaucoma, or uveitic glaucoma without further research. Considering the adverse events profile, it would not be advisable in patients with ocular surface disease
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	This could present an equivocal situation for healthcare practitioners deciding whether to prescribe the therapy over an alternative. For patients, the experience may also be equivocal, depending on the bottle used. Some bottles may be harder or easier to use than others, which is particularly relevant for patients with osteoarthritis in their hands, as they might find certain drop bottles more challenging to administer. Similarly, if any of the adverse events described in the

acceptability or ease of use or additional tests or monitoring needed)	submission occur, the therapy may be perceived as either worse or better than other alternatives with a poorer side effect profile.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There are no specific rules, but generally, this would apply in cases where pressure reduction is insufficient (less than a 20% reduction) after selective laser trabeculoplasty (SLT) or prostaglandin analogue treatments. In such instances, these inhibitors may be prescribed as a possible second, third, or fourth therapy. This course of action would continue unless the pressure remains inadequately controlled, in which case surgery or an alternative drop therapy might be proposed. Alternatively, if adverse events occur and patients wish to explore alternatives, a change in therapy may be considered.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	I believe these benefits would be evident through long-term use, particularly concerning neuroprotection and the prevention of delayed pressure rise, which can occasionally occur despite maximal medical therapy. However, these aspects cannot be considered in current Quality-Adjusted Life Year (QALY) estimates due to the current focus on pressure outcomes.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes as discussed earlier; The proposed technology has demonstrated, in laboratory studies, the ability to reverse changes that may lead to increased intraocular pressure and optic nerve damage. This involves: 1) Reducing the contraction of the trabecular meshwork and the deposition of extracellular matrix, which contributes to elevated pressure. 2) Adjusting vascular smooth muscle to enhance retinal blood flow and reduce retinal ganglion cell death. These mechanisms offer innovative ways to prevent the progression of glaucoma. However, studies using Rho kinase inhibitors have not reported

	quantifiable data on glaucoma progression, such as visual field defects or neuroretinal rim thinning. The impact of this technology on increasing sight years and improving quality of life would need to be determined through longer-term studies.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The MERCURY 3 study revealed notable differences when Roclanda was compared to the Bimatoprost-timolol combination: - Conjunctival hyperemia was reported at 30.7% with Roclanda, compared to 9.0%. - Corneal verticillata was observed at 11.0%. - The discontinuation rate was 20.2%, whereas it was 1.9% with the Bimatoprost-timolol combination. These side effects may impact the patients' tolerance to the therapy, which could hinder their ability to adhere to the medication and consequently, limit the benefits of long-term therapeutic use. However, it's important to note that I do not have firsthand experience initiating this therapy in patients myself due to local prescribing restrictions.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The MERCURY 3 study compares Bimatoprost/timolol to Roclanda. In clinical practice, some eye drops are preferred over others due to differences in side effect profiles and clinician experience. In my practice, I would choose not to use Bimatoprost/timolol but rather Latanoprost/timolol, as I have observed that the former can result in hyperemia and injection. However, this preference may vary among clinicians. Key outcomes of interest include intraocular pressure, visual field changes, and retinal nerve fiber layer thickness, with the current evidence primarily focused on intraocular pressure. Longer-term studies would be required to assess visual field changes and retinal nerve fiber thickness, which can be undertaken to confirm long-term clinical outcomes which will be performed in Phase IV studies.

	All adverse events that I am aware of have been stated in the clinical trials.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	One real world data study has been published: https://link.springer.com/article/10.1007/s00417-022-05780-w This study evaluated 79 eyes of 47 patients. Baseline IOP was 18.7 ± 4.9 mmHg; mean change in IOP (ΔIOP) each study visit compared to baseline ranged from − 1.6 ± 3.5 to − 4.4 ± 4.1 mmHg (all $p < 0.05$). Across all study visits, conjunctival hyperemia was documented in 26 (32.9%) eyes. Subjective blurry vision was reported in 22 (27.8%) eyes without significant worsening of visual acuity at any visit (all $p > 0.05$). Six (7.6%) and 7 (8.9%) eyes required further medical or surgical/laser intervention
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could	Considering the burden of glaucoma in Afro-Caribbean populations, characterised by earlier onset and rapid progression, there is significant interest in the use of these therapies for this patient cohort. However, how the therapy responds in this specific population is yet to be determined and requires further clinical research.

• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key Issue 1: Non-systematic inclusion of monotherapy trials the network meta-analysis	
Key Issue 2: Economic model structure does not capture disease progression	
Key Issue 3: Company's assumption that those who discontinue treatment have the	

same intraocular pressure as those who remain on treatment	
Key Issue 4: Company's approach to applying health state utility values creates uncertainty	
Key Issue 5: Company's assumption of an average market share of branded and generic comparators within class, prescribed in primary care	
Key Issue 6: Company's assumption of more intensive use of secondary care resources to manage mild and moderate adverse events than would be expected in UK clinical practice	
Are there any important issues that	

have been missed in EAR?	

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Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Netarsudil-latanoprost for previously treated open-angle glaucoma or ocular hypertension [ID1363]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Friday 26 January 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

NICE National Institute for Health and Care Excellence

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating open-angle glaucoma or ocular hypertension and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Anthony Khawaja
2. Name of organisation	University College London; Moorfields Eye Hospital
3. Job title or position	Professor of Ophthalmology; Honorary Consultant Ophthalmologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with open-angle glaucoma or ocular hypertension? ☐ A specialist in the clinical evidence base for open-angle glaucoma or ocular hypertension or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.

8. What is the main aim of treatment for open-angle glaucoma or ocular hypertension? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To prevent progression and therefore irreparable damage to the vision and disability. The disability has many knock-on effects, e.g. depression, falls.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	It is well-established that every mmHg lower IOP counts and has an effect on reducing risk of future vision loss.
10. In your view, is there an unmet need for patients and healthcare professionals in open-angle glaucoma or ocular hypertension?	Absolutely there is an unmet need. Sadly, patients still lose vision and become impaired under active care. We need more treatment options that can safely lower eye pressure to reduce risk. We need drops which are effective even with lower starting pressures, and which are not difficult to adhere to (e.g. required multiple times a day) and without common systemic contraindications (e.g. asthma for beta-blockers).
11. How is open-angle glaucoma or ocular hypertension currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	We have NICE Guidelines (NG81) and our Royal College of Ophthalmologists have developed Commissioning Guidance (NICE approved process) which sets out a high value care pathway. Guidance is less prescriptive for advancing patients and there may be variability in treatment approach between clinicians (some will be more aggressive surgically than others, for example). Netarsudil-latanoprost would given another medical treatment option for patients. This could help adherence given the once daily dosing. It could help lower pressure even with low starting pressures due to its mode of action. It can also help further lower pressure even when using other drops, as the mode of action is complementary. This drop may enable some people not ideal candidates for surgery to avoid surgery.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This would fit in easily as just another medication option. It is combined with the commonest glaucoma medication (latanoprost) already. The cost seems equivalent to other branded drops. This should be easy/smooth to implement.

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	We have already approved the medication on our formulary at Moorfields and have been using for several months. It has been smooth with no issues.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	I do expect clinically meaningful benefits and have already seen this in my patients. I don't expect it to increase life, but I do expect it to preserve vision and increase health-related quality of life for appropriate patients. Given it's unique and complementary properties to current medications, this offers additional potential to slow or stop glaucoma's irreparable damage to the optic nerve and vision.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	More effective than other available medications - At lowering eye pressure even when the pressure starts at a low level - Lowering pressure even when already on multiple other medications (due to complementary mode of action) - As an effective fixed dose combination for people intolerant to beta-blockers (e.g. airways disease) - Higher chance of adherence with once daily dose It does frequently cause a red eye, but this is readily reversible if troublesome, and the redness is due to vessel dilation (which is also its desired mode of action on the aqueous fluid outflow) rather than allergy or irritation.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than	It will be easier than some fixed dose combinations due to the once daily dosing. The red eye may not be tolerated by some patients.

current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It obviously won't be first-line given we should always start with just one medication. I think adding a beta-blocker would be the usual second line, but this could be second line in patients intolerant of beta-blockers.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	I am not an expert in QALYs, but I know it is notoriously hard to put a value on the impact of blindness, and we may well underestimate the harms.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This is definitely a welcome innovation: - Alternative mode of action – all other drops work in one of two ways, and finally we have something that works in a complementary way. - This means that the drop has impressive efficacy even when the patient is already using multiple other drops. This is not the case currently, as after two drops, additional drops work in the same way without much additional effect measurable. - Because of likely effects on the distal outflow system, this lowers the "floor" of the IOP, allowing good % lowering even with lower starting pressures. This makes it particularly effective for patients with normal-tension glaucoma (around 40-50% of POAG), or for patients that are particularly vulnerable to pressure and are progressive despite low pressures.

	- Having another combination drop with once daily dosing is very helpful for maximising patient adherence, especially in our ageing population.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Red eye is a known common side effect, but this is considered non-serious as it is not an allergy and is not generally uncomfortable. It is quickly reversible. This will be intolerable for some patients, but others are very willing to have a red eye to save their vision or avoid the risks of surgery.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I think the trial versus bimatoprost-timolol is a good one, as this is likely one of the most efficacious fixed dose combination drops. IOP is universally used as a surrogate end-point for these types of study, as it is the cardinal mediating factor for glaucoma, and given the relatively slowly progressing nature of much glaucoma, trials would require very long follow-up to use a harder end-point of visual function. IOP is used as the outcome of choice for the FDA. Studies with IOP as the outcome are the basis for almost all our glaucoma treatments.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Only my personal experience (only a few months), but also the 5 year experience of US colleagues who I have engaged with. The general impression is that it can achieve impressive pressure lowering, even when on other medications or with a low starting pressure, but fairly often with a red eye
22. How do data on real-world experience compare with the trial data?	The data presented to me generally has a lower incidence of red eye than the trial data.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	If anything, this helps reduce inequalities by providing a once daily effective treatment which may be better adhered to by vulnerable patients or their carers.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key Issue 1: Non-systematic inclusion of monotherapy trials the network meta-analysis	I am not an expert on this, but it seems that there is quite some noise for the final comparisons. Clinically, I have no doubt of its effectiveness based on my experience so far.
Key Issue 2: Economic model structure does not capture disease progression	As detailed above, the vast majority of our current treatments have been evidenced by studies using IOP as the outcome. The FDA supports this.
Key Issue 3: Company's assumption that those who discontinue treatment have the	

same intraocular pressure as those who remain on treatment	
Key Issue 4: Company's approach to applying health state utility values creates uncertainty	
Key Issue 5: Company's assumption of an average market share of branded and generic comparators within class, prescribed in primary care	For me, the price of the medication seems reasonable given it is a new addition and in comparison to how drops were priced as branded and before they went generic. In fact, it seems on the cheaper side for something so unique on the market.
Key Issue 6: Company's assumption of more intensive use of secondary care resources to manage mild and moderate adverse events than would be expected in UK clinical practice	
Are there any important issues that	

have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Glaucoma patients continue to become visually impaired under our care and we need new and complementary treatments.
The complementary mode of action means this drop works well as an additional therapy
Data suggests the drop works well even with a low starting pressure, which is desperately needed as it can be hard to treat low pressures.
The once daily dosing is likely to maximise adherence and make this a suitable option for frail patients or those that need carers.
Red eye is the main downside, but this is quickly reversible if not tolerated, and patients may prefer this to losing vision or taking the risks of surgery.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Netarsudil-latanoprost for previously treated open-angle glaucoma or ocular hypertension [ID1363]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with open-angle glaucoma or ocular hypertension or caring for a patient with open-angle glaucoma or ocular hypertension. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Patient expert statement

The deadline for your response is **5pm** on **Monday 29 January 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with open-angle glaucoma or ocular hypertension

Table 1 About you, open-angle glaucoma or ocular hypertension, current treatments and equality

1. Your name	Joanna Hodgkinson
2. Are you (please tick all that apply)	☐ A patient with open-angle glaucoma or ocular hypertension? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with open-angle glaucoma or ocular hypertension? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Glaucoma UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

Patient expert statement

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with open-angle glaucoma or ocular hypertension? **If you are a carer (for someone with open-angle glaucoma or ocular hypertension) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for open-angle glaucoma or ocular hypertension on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for open-angle glaucoma or ocular hypertension (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of netarsudil-latanoprost over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**	

9c. Does netarsudil-latanoprost help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	
10. If there are disadvantages of netarsudil-latanoprost over current treatments on the NHS please describe these. For example, are there any risks with netarsudil-latanoprost? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from netarsudil-latanoprost or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering open-angle glaucoma or ocular hypertension and netarsudil-latanoprost? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key Issue 1: Non-systematic inclusion of monotherapy trials the network meta-analysis	
Key Issue 2: Economic model structure does not capture disease progression	
Key Issue 3: Company's assumption that those who discontinue	

Patient expert statement

treatment have the same intraocular pressure as those who remain on treatment	
Key Issue 4: Company's approach to applying health state utility values creates uncertainty	
Key Issue 5: Company's assumption of an average market share of branded and generic comparators within class, prescribed in primary care	
Key Issue 6: Company's assumption of more intensive use of secondary care resources to manage mild and moderate adverse events than would be expected in UK clinical practice	
Are there any important issues that	

Patient expert statement

have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Netarsudil-latanoprost for previously treated open-angle glaucoma or ocular hypertension [ID1363]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with open-angle glaucoma or ocular hypertension or caring for a patient with open-angle glaucoma or ocular hypertension. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Patient expert statement

The deadline for your response is **5pm** on **Monday 29 January 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with open-angle glaucoma or ocular hypertension

Table 1 About you, open-angle glaucoma or ocular hypertension, current treatments and equality

1. Your name	Julia Margetts
2. Are you (please tick all that apply)	☒ A patient with open-angle glaucoma or ocular hypertension? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with open-angle glaucoma or ocular hypertension? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Glaucoma UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

Patient expert statement

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with open-angle glaucoma or ocular hypertension? **If you are a carer (for someone with open-angle glaucoma or ocular hypertension) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for open-angle glaucoma or ocular hypertension on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for open-angle glaucoma or ocular hypertension (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of netarsudil-latanoprost over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**	

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13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key Issue 1: Non-systematic inclusion of monotherapy trials the network meta-analysis	
Key Issue 2: Economic model structure does not capture disease progression	
Key Issue 3: Company's assumption that those who discontinue	

Patient expert statement

treatment have the same intraocular pressure as those who remain on treatment	
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Key Issue 6: Company's assumption of more intensive use of secondary care resources to manage mild and moderate adverse events than would be expected in UK clinical practice	
Are there any important issues that	

Patient expert statement

have been missed in EAR?	

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In up to 5 sentences, please summarise the key messages of your statement:

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- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
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Thank you for your time.

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Netarsudil-latanoprost for previously treated open-angle glaucoma or ocular hypertension [ID1363]

EAG critique of company response to Technical Engagement

Produced by Aberdeen HTA Group

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Neil Scott[2]
Mohammad Azharuddin[1]
Moira Cruickshank[3]
Miriam Brazzelli[2]

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2 Medical Statistics Team, University of Aberdeen, UK
3 Health Services Research Unit, University of Aberdeen, UK

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University of Aberdeen, Health Economics Research Unit
Foresterhill, Aberdeen, AB25 2ZD
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Date completed: **02 February 2024**

Contains: [redacted]

Version: **1**

Overview

This report provides the EAG's brief commentary and critique of additional clinical, NMA and economic evidence and modelling submitted by the company Santen Pharmaceuticals, received by the EAG on January 23rd, 2024 in response to the Technical Engagement and in advance of the first AC meeting for this appraisal. Further updated versions of the economic model were sent to the EAG on January 31st and February 1st, addressing model errors and integrating all versions of the economic model into a single model file. The commentary and critique provided below should be read in conjunction with the company's submitted technical engagement response, and the EAG report. This commentary addresses each of the six issues for technical engagement in turn.

Issue 1: Clinical Effectiveness Evidence

The company's response to Technical Engagement (January 2024) contained their third analyses of clinical effectiveness following those provided in the original submission (July 2023) and in the response to clarification (October 2023).

The EAG's principal concern with the October 2023 network meta-analysis (NMA) was that the inclusion of monotherapy studies and comparators was not systematic and did not appear to follow clear pre-specified criteria. As there was no connected network including fixed dose combination (FDC) therapies, the company included selected monotherapy trials to identify the first feasible bridge connecting the two existing networks. This was described by the company as a pragmatic approach, but results from this kind of analysis may be vulnerable to bias. The EAG noted that the number of eligible monotherapy trials was likely to be large and advised that, if there was insufficient time to include all monotherapies in the timescale of NICE process, options included exploring inclusion of a subset of monotherapies using predefined criteria or restricting the eligible studies by date range or other systematic factor.

The company's approach for the January 2024 analyses was to identify an alternative network of evidence that was not reliant on a single connection via latanoprost. Five additional studies were considered, but as previously this was not the only way that studies could have been chosen to form additional connections between different parts of the network.[1-5]

The company regard the new analysis as a sensitivity analysis to the previous October 2023 NMA. The methodology remains the same as previously and, following the EAG's request, a table of data used in the NMA, and other information have now been made available. Figures 1 and 2 show the updated network diagram before and after study exclusion. Of the five additional studies, only one (Fechtner 2004)[2] was included in the company's analyses. This study provided an additional connection between latanoprost and dorzolamide-timolol. However, only one of two studies reported in the Fechtner 2004 publication, Study 1, which recruited patients from the United States (n=256), was included. The other, Study 2, which recruited patients from 11 European countries and Israel (n=288) was not included in the analyses.

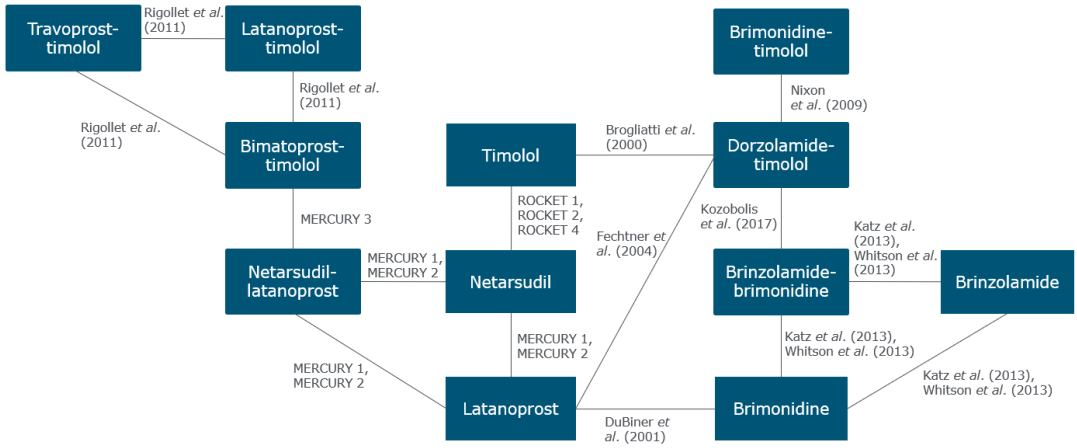

Figure 1: Connected evidence network before study exclusion [Reproduced from Figure 1, p.5 from the company's response to Technical Engagement]

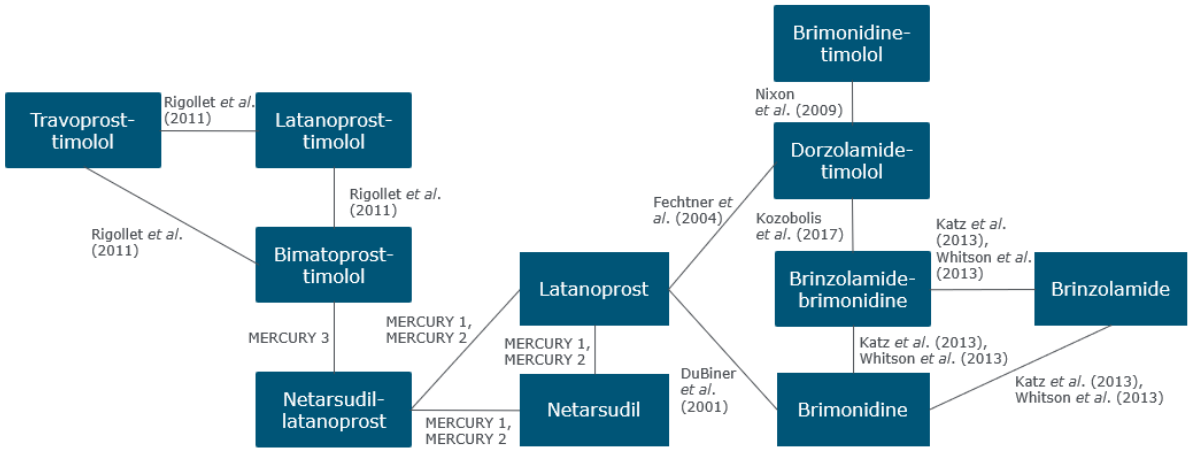

Figure 2: Restricted evidence network [Reproduced from Figure 2, p.11 from the company's response to clarification]

Brogliatti 2000,[1] which along with three other studies (ROCKET 1, ROCKET 2 and ROCKET 4)[3-5] enabled a connection between netarsudil and dorzolamide-timolol via timolol, was dropped from the analyses because data were only collected at one month post-baseline. The company then also dropped the three ROCKET studies as they contributed only to a "dead end" connection between two monotherapies (netarsudil and timolol).

The only other change to the network was the inclusion of all three arms of the MERCURY 1 and MERCURY 2 studies.[6, 7] Previously, only the netarsudil-latanoprost and latanoprost arms were considered. Now, the inclusion of the netarsudil arm provides an additional loop via this monotherapy.

The feasibility of the revised NMA was carefully considered by the company by considering the study design, the baseline participant characteristics and the definitions of comparators and outcomes in each study. Based on this assessment it was decided that it was acceptable to proceed with the NMA. The outcome used in the analysis remained the percentage change in intraocular pressure (IOP) from baseline to three months.

The results of the new NMA were similar to those in the previous analysis. When compared with all other comparators netarsudil-latanoprost had a treatment effect which was close to zero but with wide credible intervals (CrIs). As netarsudil was now included as a comparator, an additional comparison was available for netarsudil-latanoprost versus netarsudil. As previously, the company interpreted these results as an indication that all the FDC treatments had similar efficacy and that it was therefore acceptable to make this assumption in the cost-effectiveness analyses.

EAG critique of clinical effectiveness evidence (Issue 1)

The EAG was expecting that the updated evidence would follow the general principles of systematic reviews, but the company does not appear to have used a fully systematic approach leading to uncertainty about the reliability of the findings. The only change was to add Fechtner 2004 and the netarsudil arms of MERCURY 1 and 2 and there is still a lack of transparency regarding why only these studies were chosen and why netarsudil was included as an additional comparator. The non-systematic selection of studies and comparators represents a potential bias and a threat to the reliability of results.

The experience of the initial submission suggested that attempts to perform matched indirect comparison analyses of FDCs alone would be problematic. The EAG, therefore, believes that an NMA also including monotherapies is likely the best way forward. However, as the published literature on monotherapies is vast, the scope of such an NMA needs to be carefully considered. Alternative approaches, given the time limitations of the NICE process, could include restricting inclusion to certain types of monotherapies using a systematic process.

To give some examples, the EAG's information expert has conducted an initial search and

identified 60 randomised controlled trials (RCTs) of FDCs that include latanoprost, and 25 RCTs of latanoprost as a monotherapy, although he would expect these numbers to rise if extended to a full systematic search. However, a similar search for netarsudil trials yielded a much smaller number of RCTs. This suggests that a systematic review restricted to specific monotherapies may be feasible.

A further consideration is whether an analysis of netarsudil-latanoprost versus all FDCs is necessary as there is already a connected network between netarsudil-latanoprost and three of the six FDCs in the current network (travoprost-timolol, latanoprost-timolol and bimatoprost-timolol). This will depend on the importance placed by the Committee on the FDCs on the right-hand side of the network diagram (brimonidine-timolol, dorzolamide-timolol and brinzolamide-brimonidine).

As in the previous analysis, the PICO (participants, interventions, comparators, outcomes) criteria for the review were not always well defined. An additional criterion for the participants in the new analysis appears to be geographic location. One of the two studies (Study 2) reported in Fechtner 2004 was excluded from the NMA as some non-western participants may have been included (according to this publication recruits were from 11 unspecified European countries plus Israel).[2] Meanwhile, the other study (Study 1) with recruits from the United States was included in the NMA. The EAG does not think geographic location is a valid reason for excluding this study.

Four studies were excluded from the analysis because Brogliatti 2000 collected data at one month instead of three months.[1] Pre-specified information on inclusion criteria for time point was not provided.

The NMA outcome was defined as the difference in percentage change in IOP between baseline and three months. As previously noted, the EAG's clinical advisers agree that this is the most clinically relevant definition of outcome, but it does make the conduct of the NMA more challenging as most studies reported only IOP at baseline and three months. This meant that simulations had to be conducted to calculate percentage change and its standard error, based on the baseline and three-month data reported in the trial publications. This introduces additional assumptions that would not have been necessary if the outcome had been defined as IOP at three months as in other NMAs in this area.

In this submission the company provided greater detail about how the NMA was conducted. This included a table on the derivation of mean and SE/SD diurnal IOP when multiple times of day are reported (Table 24), and a table of data input for the NMA at baseline and three months (Table 25). R code for simulating percentage change from baseline and follow-up IOP data was also provided. The EAG welcomes this additional information, but it has been unable to fully scrutinise it due to the short timeframe of the Technical Engagement process.

We would like to mention the following as points of current concern.

Based on a comparison of selected study publications with the information presented in Tables 24 and 25, the EAG believes that the columns labelled as representing standard error (SE) in Tables 24 and 25 represent standard deviation (SD) instead, particularly as SD is also referred to on page 12 and in the "Data manipulation required" column of Table 24. The supplied R code for calculating percentage change also uses both terms and the EAG is concerned with the possibility that mislabelled or incorrect data may have been used in the NMA. The final table of data used in the NMA does not seem to be supplied.

Figures 4 and 5 of the Technical Engagement submission and the text below these figures refer to "percentage change in diurnal IOP from baseline". However, when checking the data tables and original study data it seems more likely that the effect size is defined using an IOP difference expressed as a proportion, as described in the sentences interpreting the results for netarsudil-latanoprost versus netarsudil.

Assuming this interpretation is correct, for example, the corresponding result for netarsudil-latanoprost versus brimonidine-timolol ([redacted]) implies that netarsudil-latanoprost was associated with a reduction in IOP that was [redacted] percentage points lower than the reduction for brimonidine-timolol, but with a credible interval (CrI) from [redacted] points lower to [redacted] points higher, reflecting a high degree of uncertainty. Therefore, the EAG remains concerned about the validity of the assumption used by the company in the cost-effectiveness analyses that netarsudil-latanoprost has the same efficacy as other FDCs in the network.

In summary, the EAG still has important concerns about the clinical effectiveness evidence. Due to the non-systematic selection of studies, the results of the NMA could be affected by

bias and there are concerns about the arbitrary inclusion or exclusion of certain data (e.g., Study 2 of Fechtner 2004)[2] in the analyses. The report also has internal inconsistencies (SD versus SE, percentage change versus proportions) which means there is uncertainty as to whether the conclusions are valid. Assuming that the company's interpretation of the results is correct, there is considerable uncertainty around the NMA estimates. Therefore, the EAG is not convinced that all FDCs have the same effect. This has implications for the economic modelling because an assessment of the treatment alternatives based on cost alone would require an assumption of similar effectiveness. Based on these considerations, the results of this section should still be interpreted with caution.

Issue 2: Economic model structure not capturing disease progression.

In response to technical engagement, the company have revised their base case economic model to apply a 1 year, rather than a lifetime horizon. The company claim that this adaption mitigates EAG concerns that the model structure (and health states defined by short-term changes in IOP, rather than glaucoma disease progression) is not sufficient to capture all relevant costs and benefits over a lifetime horizon. The company further claim that the treatment indication for netarsudil-latanoprost (POAG or OHT) is suitable for evaluation using a short time horizon model. The company also justify using a shorter-term time horizon because there is limited data to establish a link between short- and long-term disease progression and thus a shorter time horizon avoids the need to make unrealistic assumptions and extrapolations.

The EAG position post-technical engagement remains unchanged concerning the appropriateness of the economic model structure. Health states defined according to IOP are intermediate states and the model does not adequately map changes in IOP to an associated impact on conversion from OHT to glaucoma or progression of glaucoma disease. The EAG are, therefore, of the view that to conduct a robust assessment of cost-effectiveness, for netarsudil-latanoprost against all comparators, a lifetime-modelled time horizon is required, using an economic model that adequately captures conversion from OHT to glaucoma and progression of glaucoma over time. The EAG continues to be of the view that it would have been possible to develop such a model for this assessment. Several such examples have been referred to in Table 10 of the EAG report. Indeed, the EAG suggested an alternative structure, detailing potential Markov states defined by OHT and COAG stage re-produced in Figure 3 below.

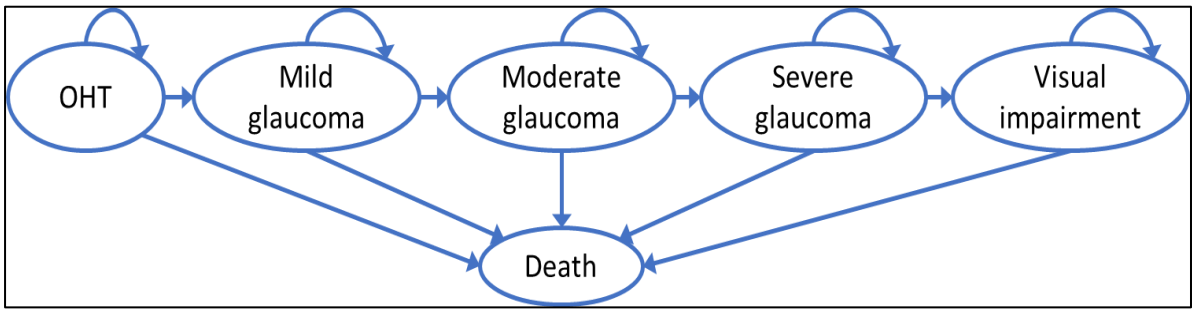

Figure 3 EAG suggested model structure.

The EAG disagree with the company argument that OHT and glaucoma are not suitable for a life-time horizon model. Glaucoma is a chronic condition that progresses over time, can ultimately lead to blindness, and often requires multiple lines of treatment, up to and including surgery. To capture all the relevant costs and outcomes of the impact of reducing IOP on glaucoma disease progression, a lifetime horizon model is essential. The only scenario where a lifetime model might not be required is when there is clear evidence that interventions and all comparators provide equivalent outcomes (e.g. change in IOP). This could be demonstrated using a high-quality systematic review and network meta-analysis that shows clear evidence of similar outcomes and excludes clinically meaningful differences. The EAG report noted that such evidence was not available for all comparators, due to concerns with the completeness of the company's NMA. Based on the critique provided under Issue 1 above, the EAG is not satisfied that sufficient evidence has been provided to demonstrate equivalence of outcomes across comparators.

As detailed in the EAG report, a short-term horizon assessment of costs is not appropriate when there is substantial uncertainty surrounding the incremental benefits of one treatment over another. The EAG does however acknowledge that for a comparison of netarsudil-latanoprost vs. bimatoprost-timolol, based on data from the MERCURY trial the uncertainty surrounding an assumption of similar outcomes is somewhat reduced. Whilst there are some statistically significant effectiveness differences between groups in favour of bimatoprost-timolol, the EAG's clinical expert advisors did not consider these to be of a clinically meaningful magnitude. As was provided in the EAG report, several exploratory analyses comparing netarsudil-latanoprost and bimatoprost-timolol are provided for the committee's information over a shorter 1-year time horizon where the implications of an inappropriate model structure are minimized. Whether these analyses are suitable for decision making requires a judgement on whether the differences are sufficient to rule out clinically

meaningful differences and whether bimatoprost-timolol is the only relevant comparator for the assessment.

The company further support their position with reference to previous NICE TAs that may have adopted a non-lifetime horizon, specifically (NICE TA471, TA217, and TA729 for irritable bowel syndrome, Alzheimer's disease, and hyperphenylalaninaemia in phenylketonuria respectively).[8-10]

The EAG raise concerns with the company's comparison of the case of this appraisal with previous NICE TAs for different indications, justifying shorter time horizons. For example, TA471 for irritable bowel syndrome has been withdrawn and so is not relevant.[8] TA111, originally published in 2006, assessed the cost-effectiveness of donepezil, galantamine, rivastigmine, and memantine in Alzheimer's disease.[11] Subsequently, it has been updated and replaced by TA217.[9] In the case of TA217, the manufacturer of donepezil (Eisai/Pfizer) and the manufacturer of memantine (Lundbeck) both submitted a discrete event simulation and Markov cohort model.[9] These models evaluated the cost-effectiveness of donepezil and memantine compared to best supportive care over a lifetime (25-year) time horizon and 5-year time horizon in people with mild to moderate and moderate to severe Alzheimer's disease respectively and as such a lifetime horizon has been adopted. The manufacturers of galantamine and rivastigmine did not submit any new economic models. However, the EAG for that assessment considered the base case lifetime horizon (20 years) to be more appropriate to evaluate the cost-effectiveness of the AChE inhibitors for mild to moderate disease. Whereas memantine was not included in the EAG base case for mild to moderate disease. Considering the EAG position, NICE recommended donepezil, galantamine, and rivastigmine as monotherapy options for managing mild to moderate Alzheimer's disease within certain conditions. On the other hand, memantine monotherapy is recommended as an option for individuals with moderate Alzheimer's disease who cannot tolerate or have contraindications to AChE inhibitors, or for those with severe Alzheimer's disease. Regarding TA729, the ERG raised initial concerns about the initial model presented by the company over lifetime horizon. Following TE, the company submitted a revised decision tree model with a 1-year time horizon to assess the cost-effectiveness of sapropterin in combination with a protein-restricted diet versus a protein-restricted diet alone, incorporated three health states for each group based on symptom severity, including mild, moderate, and severe. Following this, sapropterin is recommended as a treatment option for

hyperphenylalaninaemia responsive to sapropterin in individuals with phenylketonuria (PKU), under the certain conditions. The EAG therefore remains unconvinced that the quoted TAs provide sufficient justification for the shortened time horizon.

In summary, the EAG are of the view that a full lifetime horizon model should have been built for this assessment, with health states defined that adequately capture the full cost and benefit implications of reductions in IOP on slowing the rate of conversion from OHT to glaucoma, and slowing disease progression for patients who have glaucoma. Such a model could have been built and parameterised based on data from the literature, using examples of other glaucoma decision models referenced by the EAG. That approach would have reduced uncertainty for decision making. Given the lack of evidence to support equivalence between netarsudil-latanoprost and all relevant comparators from the NMA, the EAG remains unconvinced that an assumption of equivalent effectiveness compared to any comparator except bimatoprost-timolol can be justified.

Issue 3: Company's assumption that those who discontinue treatment have the same intraocular pressure as those who remain on treatment.

The EAG report raised a concern that the company's economic model assumed that treatment discontinuation had no impact on health state transition probabilities, health state occupancy or hence modelled QALYs. The EAG view, consistent with several other published economic models, is that treatment discontinuation might occur due to adverse events but might also occur due to a lack of effectiveness. Assuming no impact on QALY gains is inconsistent with a disease pathway which may require multiple lines of treatment, up to and including surgery. This issue is related to issue 2, in so far as the model structure does not capture the impact of disease progression, either through increasing health state severity over time, or increasingly invasive lines of treatment.

In response to Technical Engagement, the company's solution to this problem has been to exclude treatment discontinuation entirely from the model, instead assuming that participants remain on their index treatment for a time horizon calculated from the originally submitted model file. There is no second line of treatment modelled and the company has also removed all costs of surgery from the model. The revised modelled time horizon for treatment discontinuation is calculated as the median modelled time to treatment discontinuation

observed from the lifetime horizon model, weighted according to company market share for each treatment class. This results in a time horizon of 15 (monthly) cycles, (See Table 5 of company's TE response). This is then over-ridden with a time horizon of one year on the justification that there is wide variation in the median time to discontinuation across comparators.

The EAG are concerned that the rationale for choosing a model time horizon calculated as the median time to treatment discontinuation is not well justified and has not been supported by clinical validation. Such an approach retains all the limitations of an inappropriate model structure, and further increases potential for bias by removing an important consideration from the care pathway, where patients will have multiple lines of treatment over time based on their disease stage. The EAG also does not consider it appropriate to exclude the costs of surgery from the model. Indeed, surgery may form a crucial part of the treatment pathway in later stages of glaucoma disease.

The EAG notes that the calculated model time horizon has been over-ridden for the base case to apply a time horizon of one-year. However, this would only be an appropriate scenario for consideration if equivalence could be adequately demonstrated across all FDC comparators. Given the EAG's significant concerns with the clinical effectiveness review and NMA raised in issue 1, there remains too much uncertainty for the EAG to support the use of a one-year time horizon. Therefore, the EAG does not consider the company's approach to be appropriate for decision making.

The company further attempt to justify the removal of treatment discontinuation from the model on the grounds that differences in treatment discontinuation between netarsudil-latanoprost and bimatoprost-timolol observed in the MERCURY 3 study not representative of the UK POAG/OHT population. The company claim that observed differences are driven by the protocol for the MERCURY 3 study, where patients were required to not be treatment naïve or present any sensitivity to investigational formulations. This implies that the company are assuming that the UK POAG / OHT population treated with bimatoprost-timolol might be treatment naïve or have tolerance issues. The company support their claim by providing data comparing the annual rate of adverse events experienced by bimatoprost and timolol patients in MERCURY 3 vs. those in alternative studies (See Table 6 of company's TE response). The data show an annual bimatoprost-timolol discontinuation rate varying between 12.26% in

MERCURY 3 and 25.66% in an alternative study with six-month follow-up in a Chinese population.

The EAG does not consider the company's argument to be sufficient to ignore the randomised data from the MERCURY 3 trial. MERCURY 3 provides the best available comparative data for treatment discontinuation on netarsudil-latanoprost vs. bimatoprost-timolol. Comparative variation in discontinuation rates from real world evidence has not been provided for netarsudil-latanoprost, meaning that the difference in treatment discontinuation rates between NL and BT in a real-world setting cannot be ascertained.

Furthermore, the EAG disagrees with the company's statement regarding the use of bimatoprost-timolol in patients with POAG or OHT who are treatment-naïve or have tolerance issues. The EAG contends that this terminology is misleading, as the marketing authorisation for Ganfort specifies the indication for adults with POAG or OHT who are insufficiently responsive to topical beta-blockers or prostaglandin analogues (other medicines used for these conditions). By definition, they are not treatment naïve and as such the trial use of bimatoprost-timolol is consistent with the marketing authorisation.

The company also claim that participants in the MERCURY 3 trial did not receive bimatoprost-timolol if they had sensitivity to the treatment. Although not explicitly stated in the company document, this implies that the company expect a substantial proportion of patients to have "sensitivity" when treated with bimatoprost-timolol in clinical practice. However, the company have not provided any data to support this claim, or any information on the proportion who were initially recruited but did not take part due to tolerance issues. Furthermore, the company have made no statements on any potential similar issues for netarsudil-latanoprost. Therefore, to make any adjustment to treatment discontinuation based on possible sensitivity to treatment for bimatoprost-timolol but not for netarsudil-latanoprost would generate a bias in favour of netarsudil-latanoprost in terms of discontinuation rates.

The EAG retains the view that the most appropriate, and non-biased source of treatment discontinuation parameters for the economic model is to use the available data from the MERCURY 3 trial. The EAG further notes that no such data have been provided for any of the other treatment comparators. The EAG also disagrees with the removal of second and

subsequent lines of treatment from the economic model because it does not reflect real-world use of FDC treatments for OHT or POAG.

Issue 4: Health state utility values

The EAG report requested a scenario analysis where SF-36 data are used to directly generate health state utility values by converting it to SF-6D and applying the SF-6D tariff. The purpose of requesting this additional scenario was to provide an alternative estimate of utility that was not necessarily exposed to the uncertainty of mapping algorithms. The company provided SF-6D utilities as a scenario analysis post technical engagement. The company explained that the SF-6D utilities showing a greater benefit in achieving a 20% improvement in IOP compared to the EQ-5D, demonstrating that the base case EQ-5D utility values may be conservative. EQ-5D values are maintained in the base case for alignment with NICE reference case. Table 1 compares the EQ-5D and SF-6D utility values.

Table 1. Health state utility values [reproduced from Table 7 of the company's TE response]

Health state	EQ-5D utility value (standard error) – reproduced from the company submission	SF-6D utility value (Standard error) – sensitivity analysis
<20% reduction in IOP	[redacted]	0.732 (0.01)
20% - 30% reduction in IOP	[redacted]	0.751 (0.01)
>30% reduction in IOP	[redacted]	0.751 (0.01)

Abbreviations: IOP – intraocular pressure; SF-6D – Short-Form Six-Dimension Questionnaire

The EAG acknowledges the additional information provided by the company. It is noted that SF-6D utility values in the model yield similar overall results to the base case EQ-5D mapped utilities. However, the EAG are of the view that any differences in short term utility associated with changes in IOP do not reflect the impact on utility of glaucoma disease progression. The EAG note that this scenario could only ever be appropriate over a very short time horizon where IOP has not resulted in glaucoma progression to capture the impact of changes in IOP on utility. However, beyond the short time horizon (one year), the scenario provided by the company holds limited value due to overall concerns with the model structure detailed in issue 2 above.

The EAG reiterate the concerns raised in the EAG report, that the company's model does not account for utility changes due to the impact of IOP (or changes in IOP) on subsequent conversion from OHT to glaucoma, or glaucoma disease progression. Health states of change in IOP and glaucoma disease progression cannot be used interchangeably, and the health state utility values included in the model do not reflect the likely quality of life of patients with mild, moderate, and severe glaucoma disease respectively.

Issue 5: Company's assumption of an average market share of branded and generic comparators within class, prescribed in primary care.

Following technical engagement, the company maintains its preference to use NHS indicative list prices for branded treatment and drug tariff prices for generic products. The company's approach is based on the proportion of treatments that are branded / generic in UK clinical practices, obtained from UK sales data from December 2015 to December 2022. The company state that the EAG's assumption for the use of generic products only is inappropriate, as this would under cost netarsudil-latanoprost comparators.

As detailed in the EAG report, post FAC, the EAG do not apply generic substitution for branded alternatives. The EAG provided scenario analyses adopt the same market share data as provided by the company. But the company and EAG disagree on the most appropriate source of prices for application in the model. The company's preferred costing approach for comparators assumes an average market share for both branded alternatives (costed using the NHS indicative prices) and generic alternatives (costed using drug tariff prices) within class, prescribed in primary care. The EAG prefers the use of drug tariff prices for all treatments. These prices more accurately capture the price paid to pharmacies for dispensing treatments in primary care and are in line with NICE's preferred hierarchy of costing sources which states "For drugs that are predominantly prescribed in primary care, prices should be based on the Drug Tariff".[12] The EAG, therefore, prefer to apply the drug tariff price from the BNF for all treatments in primary care. If the committee were interested in the costs of prescribing in secondary care, the EAG's preferred source would be eMIT prices. However, the EAG and company are both in agreement that most prescribing will take place in primary care. Table 3 below details the company and EAG preferred costing source assumptions for primary care prescribing, using the company corrected economic model.

Table 2 Comparison of different treatment acquisition costs for application in the economic model

Active ingredient	Product name (if not generic)	Product specific	Company Market share (%)	NHS indicative price (£)	Drug tariff price (£)	eMIT price (£)	Company preferred weighted average cost per cycle in primary care (£) *(NHS indicative price for branded and DTP for generic)*	EAG preferred weighted average cost per cycle in primary care (£) *(Drug tariff prices for all)*
Brinzolamide & timolol	Azarga	Azargaeyedr5/10mg5ml	[redacted]	11.05	4.04	4.04	£7.34	£4.24
	Generic	TIMOLOL/BRINZOLAMIEYEDR5/10MG5ML	[redacted]	8.19	3.17	4.04		
Dorzolamide & timolol	Generic	Dorzolamid/timololeyedrops2%60.2ml	[redacted]	28.59	17.86	22.15	£9.56	£6.52
	Generic	DORZOL/TIMOLOLSDZEYEDROPS5ML	[redacted]	1.86	1.7	2.41		
	Generic	DORZOL/TIMOLOL ZVA EYE DROPS 5ML	[redacted]	1.86	1.7	2.41		
	Generic	DORZOLAMID/TIMOLOL EYE DROPS 5ML	[redacted]	1.86	1.7	2.08		
	COSOPT	COSOPTEYEDROPS5ML	[redacted]	10.05	1.7	2.41		
	COSOPT	COSOPTMSDEYEDROPS5ML	[redacted]	10.05	1.7	2.41		
	COSOPT	COSOPTEYEDROPU/D60.2ML	[redacted]	28.59	17.86	22.15		
	COSOPT	COSOPTIMULTIEYEDROPS10ML	[redacted]	28	28	4.82		
	EYLAMDO	EYLAMDOPFEYEDROPS5ML	[redacted]	8.13	8.13	2.41		
	VIZIDOR	VIZIDORDUOPFEYEDROPS5ML	[redacted]	8.14	8.13	2.41		
Latanoprost & timolol	Generic	Latanoprost/timoleyedrops2.5ml	[redacted]	3.52	5.2	2.03	£12.22	£7.79
	Generic	LATANOPROST/TIZVAEYEDROPS2.5ML	[redacted]	3.52	5.2	2.03		

Active ingredient	**Product name (if not generic)**	**Product specific**	**Company Market share (%)**	**NHS indicative price (£)**	**Drug tariff price (£)**	**eMIT price (£)**	**Company preferred weighted average cost per cycle in primary care (£)** ***(NHS indicative price for branded and DTP for generic)***	**EAG preferred weighted average cost per cycle in primary care (£)** ***(Drug tariff prices for all)***
	Generic	LATANOPRST/TIMSDZEYEDROPS2.5ML	[redacted]	3.52	5.2	1.58		
	FIXAPOST	FIXAPOSTPFE/DUDV30.2ML	[redacted]	13.49	13.49	13.49[A]		
	MEDOX	MEDOX50MCG/5MG/ML2.5ML	[redacted]	14	3.47	2.03		
	XALACOM	XALACOMEYEDROPS2.5ML	[redacted]	14.32	5.2	2.03		
Tafluprost & timolol	Taptiqome	Taptiqome/d15y&5mg30.3ml	[redacted]	14.5	14.5	14.50 [A]	£14.71	£14.71
Bimatoprost & timolol	Generic	Bimatopro/timozvaeyedrops3ml	[redacted]	14.16	14.16	14.16 [A]	£15.82	£15.82
	Generic	BIMATOPROST/TIMOLOEYEDROPS3ML	[redacted]	14.16	14.16	14.16 [A]		
	EYZEETAN	EYZEETANEYEDROPS3ML	[redacted]	14.16	14.16	14.16 [A]		
	GANFORT	GANFORTEYEDROPS33ML	[redacted]	14.16	14.16	14.16 [A]		
	GANFORT	GANFORTEYEDROPS3ML	[redacted]	14.16	14.16	14.16 [A]		
	GANFORT	GANFORTVIALSU/D30.4ML	[redacted]	17.94	17.94	17.94 [A]		
Travoprost & timolol	Generic	Travoprosttimololeye/dropsol2.5ml	[redacted]	6.75	4.51	4.51 [A]	£12.18	£5.49
	DUOTRAV	DUOTRAVEYE/DROPSOL2.5ML	[redacted]	13.95	4.51	4.51 [A]		
Brinzolamide & Brimonidine	SIMBRINZA	Simbrinza 10mg/ml / 2mg/ml eye drops	[redacted]	9.23	9.23	9.23 [A]	£11.24	£11.24

Active ingredient	**Product name (if not generic)**	**Product specific**	**Company Market share (%)**	**NHS indicative price (£)**	**Drug tariff price (£)**	**eMIT price (£)**	**Company preferred weighted average cost per cycle in primary care (£)** ***(NHS indicative price for branded and DTP for generic)***	**EAG preferred weighted average cost per cycle in primary care (£)** ***(Drug tariff prices for all)***
Brimonidine & timolol	Combigan	Combiganeyedrops35ml	[redacted]	27	27	27.00 [A]	£12.60	£16.23
	COMBIGAN	COMBIGANEYEDROPS5ML	[redacted]	10	13.22	13.22 [A]		

[A] Drug tariff prices are assumed in cases where eMIT prices are not available.

Issue 6: Company's assumption of more intensive use of secondary care resources to manage mild and moderate adverse events than would be expected in UK clinical practice.

In the revised post technical-engagement model, the company has further adjusted the unit cost of managing adverse events. They have achieved this by:

A) Splitting all adverse events in each arm of the MERCURY-3 trial according to severity (mild, moderate, severe).
B) Calculating a weighted average proportion of adverse events that are mild, moderate, and severe, pooled across treatment arms.
C) Using the weighted average from B above, costs are applied by grade of severity as follows:
    a. Mild adverse events are assumed to cost £0.
    b. Moderate adverse events are assumed to incur the EAG preferred unit costs (See EAG report Table 15).
    c. Severe adverse events are assumed to incur the company original preferred unit costs (See EAG report Table 15).
D) The final unit cost, per adverse event is calculated by multiplying B x C.

The EAG note that the company have attempted to account for severity of adverse events within their unit cost calculations. The EAG accepts that many adverse events are mild and would not incur resource usage. Nevertheless, the company's approach should not be interpreted as accounting for any differences in severity of adverse event across comparator arms of the model, because the weighted average cost is applied to the rate of all adverse events, regardless of severity. The EAG note that incremental adverse event costs are broadly similar according to the company's revised approach and the EAG preferred approach. The decision on whether to accept the company revised or EAG approach has little impact on overall results. Total average costs per cycle are summarised in Table 3 below, comparing the company's original approach, EAG preferred approach and company approach post technical engagement.

Table 3 Comparison of EAG and company preferred AE resource use assumptions.

		Roclanda	Brinzolamide and timolol	Dorzolamide and timolol	Latanoprost and timolol	Tafluprost and timolol	Bimatoprost and timolol	Brimonidine and timolol	Travoprost and Timolol	Brinzolamide and brimonidine
Company original	1	[redacted]	£33.40	£42.93	£32.04	£38.43	[redacted]	£56.62	£36.26	£43.93
	2	[redacted]	£30.44	£39.97	£31.92	£37.67	[redacted]	£48.36	£35.50	£35.66
	3	[redacted]	£21.50	£29.88	£23.81	£24.10	[redacted]	£26.45	£19.21	£15.53
	4+	[redacted]	£0.00	£0.01	£5.42	£5.41	[redacted]	£0.01	£5.42	£0.00
EAG	1	[redacted]	£7.17	£6.64	£9.10	£11.60	[redacted]	£15.76	£10.05	£15.51
	2	[redacted]	£6.60	£6.06	£9.09	£11.58	[redacted]	£12.54	£10.04	£12.29
	3	[redacted]	£3.04	£2.26	£6.76	£6.76	[redacted]	£4.88	£4.68	£4.37
	4+	[redacted]	£0.00	£0.00	£0.00	£0.00	[redacted]	£0.00	£0.00	£0.00
Company post TE	1	[redacted]	£0.56	£1.84	£1.79	£1.46	[redacted]	£5.92	£1.42	£6.39
	2	[redacted]	£0.49	£1.77	£1.78	£1.46	[redacted]	£3.19	£1.41	£3.66
	3	[redacted]	£0.14	£1.35	£1.18	£0.81	[redacted]	£1.00	£0.61	£0.83
	4+	[redacted]	£0.00	£0.00	£0.00	£0.00	[redacted]	£0.00	£0.00	£0.00

The EAG further notes that whilst the resource use and cost data may be complete for netarsudil-latanoprost and bimatoprost-timolol, based on data from the MERCURY 3 trial, the EAG remains concerned that there is significant residual uncertainty for the AE management cost of the remaining comparators and that the AE costs for these comparators have required multiple substantial assumptions as noted in the EAG report.

Overall summary of the EAG's critique post technical engagement

The EAG still have substantial concerns about the completeness of the clinical effectiveness review and the robustness of the company's revised NMA. Assuming the results of the NMA are correct, credible intervals are very wide demonstrating substantial uncertainty that makes it impossible to determine whether all FDC comparators are likely to be of similar effectiveness. Therefore, the EAG does not consider an assessment of costs over a one-year time-period across all FDC comparators to be appropriate because there remains too much uncertainty regarding differences in treatment benefit across comparators.

Despite concerns raised from the outset of the appraisal, the company have chosen to retain the use of a Markov model with health states defined according to intermediate change in IOP outcomes. The EAG does not consider economic modelling based on intermediate outcomes to be appropriate because it fails to capture the cost and QALY implications of the impact of changes in IOP on conversion from OHT to POAG or POAG disease progression over time. The company have reduced the time horizon to one year, removed subsequent lines of treatment from the model and assumed equal treatment discontinuation rates for all comparators. The EAG considers it essential to incorporate further lines of treatment in a chronic disease pathway that includes multiple treatment options, up to and including surgery. This might be incorporated through different treatment distributions depending on the severity of the underlying health state. Similarly, it is not appropriate to remove treatment discontinuation from the model because there is clear evidence of differences from the MERCURY 3 trial that should be incorporated.

The EAG has not conducted further scenario analyses as part of the Technical Engagement critique because any such analyses would be applied to an underlying model structure that we do not consider to be appropriate for decision making, and so any results may be misleading. The EAG is unable to identify a preferred base case ICER for this assessment.

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Netarsudil-latanoprost for previously treated open-angle glaucoma or ocular hypertension [ID1363]

EAG critique of the company submitted cost comparison

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Overview

This report provides the EAG's commentary and critique of the revised cost-comparison economic evidence and modelling submitted by the company Santen Pharmaceuticals, received by the EAG on 2 April 2024 following the first Appraisal Committee Meeting for the topic. The commentary in this critique relates to the cost comparison case made by the company and incorporates a revised treatment acquisition cost of [redacted] per pack. The EAG's previously provided critiques of the original submission and technical engagement response still apply to this assessment, in particular the critique around clinical effectiveness and uncertainty of the evidence surrounding equal treatment effectiveness across all comparators. This document should therefore be read in conjunction with these earlier reports in order to obtain a full comprehensive overview of the EAG's critique of the submission in its totality. This document raises several key issues of uncertainty that remain for this assessment, under a cost-comparison framework. These issues are addressed in the order they appear in the company submitted cost comparison template.

Issue 1: Clinical Effectiveness Evidence

No additional clinical effectiveness evidence was provided in the most recent company submission (April 2024). The reader is referred to pages 1-8 of the EAG's response to the Technical Engagement (February 2024) for an overview of the issues with the company's previous clinical effectiveness analyses. The EAG believes it is worth restating these concerns, as they are still relevant to the decision to conduct a cost comparison analysis in the most recent submission. The EAG has also been able to use the additional time to conduct a thorough critique of the R code supplied in the third set of analyses (January 2024).

Although the company's network meta-analysis (NMA) showed that netarsudil-latanoprost had similar effectiveness to other fixed dose combination (FDC) therapies, the following concerns were noted:

1) The NMA was not conducted using a robust systematic approach. In particular, the inclusion of studies and comparators was somewhat *ad hoc*. Although it is challenging to conduct an appropriate NMA in the timescale of the NICE submission process in the situation where there is no connected network, the company did not appear to follow DSU guidelines or incorporate suggestions made by the EAG, which might have allowed a more robust analysis.
2) The PICO (participants, interventions, comparators, outcomes) criteria used in the review were not completely transparent. A small subset of the available monotherapy studies was included but some studies were dropped for reasons that appear unclear or arbitrary, which could potentially result in biased estimates. For example, in the January 2024 submission only one of two monotherapy studies reported in the same publication (Fechtner 2004) was included. The included study recruited participants from the United States, but a sister study, recruiting participants from 11 European countries and Israel was excluded.
3) The only outcome evaluated was percentage change in intraocular pressure (IOP) from baseline. Although this represents an outcome that would be useful to clinicians, the published articles did not present this, so the data used in the NMA had to be derived using computer simulations using a process that assumed, without clear justification, a correlation of 0.5 between baseline and follow-up IOP.

4) The actual data used in the NMA (percentage change from baseline) were not presented. In their third submission (January 2024) the company provided data tables, but this only showed IOP at baseline and three-month follow-up.
5) In the January 2024 submission there were concerns that the company had confused standard deviation (SD) and standard error (SE) in both the data tables and the R program used to convert data to percentage change. By cross-checking against the published articles, the EAG has established that the column labelled as "SE" in Tables 24 and 25 of the Technical Engagement response actually represent SD.
6) The R program (Figure 3 of Technical Engagement response) there is also a labelling concern as certain variables are labelled "se" even though these represent SD.
7) Within the R program there appears to be an error in two places where "b[1]" is used instead of "b[i]". This means that the SD from study arm 1 is used in the covariance matrix instead of the SD from the ith study arm. This is a clear error but the impact on the results may not have a large magnitude.
8) The R program does not account for the sample size in each study arm. The EAG believes that an appropriate simulation program should incorporate a simulation of the n participants in a particular study arm within a nested loop. Tests made by the EAG suggest that, although the "y1" generated at the end of the company's program is broadly correct and could be used as an estimate of treatment effect within an NMA, the "se1" is not an appropriate SE to be used in the NMA and could be out by a factor of around 100. The company may have converted this from a SD to a SE in a separate step by dividing by the square root of the sample size for each study arm, but we cannot tell as the table of data used in the NMA has not been provided.
9) When presenting the results of the NMA on p.13-16 in the response to Technical Engagement the company includes inconsistent references to percentage change and proportion change. We are not able to check the implications of this as the final data used in the NMA were not provided, but this is another issue that has the potential to over- or under-estimate the width of the 95% credible intervals (CrIs) for the difference between netarsudil-latanoprost and the other comparators. The company interpret the wide CrIs as evidence that all FDC therapies have the same effect on IOP but the interpretation would be different depending on whether the results represent a difference in percentage or proportion change in IOP.

Overall, these concerns lead the EAG to question the validity of the assumption used in the cost comparison analyses that all therapies have the same effect.

Issue 2: Economic model structure not capturing disease progression.

The EAG report and subsequent technical engagement critique raised concerns that the economic model structure proposed by the company, with health states defined according to intermediate IOP endpoints, failed to capture all the relevant costs and benefits of glaucoma disease progression over time. For this cost comparison case, the company has proposed equivalent effectiveness, a shortened one-year model time horizon, and a revised focus on treatment acquisition and adverse event costs. Whilst the original model structure remains, the EAG agrees that the revised focus and simplified assumptions mean that the model structure does not have a major impact on results for the cost comparison case. However, this is only true if the committee is satisfied with the assumption of equal effectiveness (See Issue 1 above). Otherwise, the EAG remains concerned that the company's model structure would not be appropriate for decision making in the context of a full STA, where it is important to capture all the long-term costs and benefits of a treatment's impact on disease progression.

Issue 3: Company's assumptions regarding treatment discontinuation

The EAG were concerned that the original economic model did not fully capture all relevant cost or QALY implications of unsuccessful lines of treatments, meaning that the model predicted outcomes that had questionable face validity. For example, treatment discontinuation improved the cost-effectiveness case by reducing treatment acquisition costs with no subsequent impact on health state occupancy or associated QALY losses. In the revised modelling approach for the cost-comparison case, the company reduced the time horizon to one year, removed subsequent lines of treatment from the model, and effectively assumed that there is no treatment discontinuation for netarsudil-latanoprost or any of the comparators. Whilst the company's simplified cost-comparison approach addresses some of the concerns (e.g., around QALYs if the equal effectiveness assumption is met), the model retains limitations with regard to the treatment acquisition costs associated with treatment discontinuation.

For example, it is assumed that patients will remain on treatment for the full one-year time horizon of the revised model regardless of the treatment line they are allocated to. Whilst the

EAG agrees that the approach allows a clear comparison of treatment acquisition costs across comparators, the approach negates the fact that, in the MERCURY 3 trial, and real-world practice netarsudil-latanoprost has a less favourable adverse event profile and higher treatment discontinuation rates than, for example, bimatoprost-timolol. In the MERCURY 3 trial, 44 (20%) of participants discontinued netarsudil-latanoprost treatment due to adverse events, compared to 4 (2%) discontinuing bimatoprost-timolol (See Table 27 of the company submission). The EAG understands that it is important to consider the implications of further lines of treatment, even in a short-term model as patients may discontinue treatment early due to adverse events. This might be incorporated by adding a second line of treatment to the cost-comparison model. The EAG does not consider it appropriate to remove treatment discontinuation entirely from the model because there is clear evidence from the MERCURY trial of treatment discontinuation rate differences between trial groups that should be incorporated in the analysis. The impact of early discontinuation on incremental costs is likely to depend on the costs of netarsudil-latanoprost relative to the costs of treatments that might be included at the next treatment line.

Issue 4: Health state utility values

Issues around health state utility values are no longer an important consideration if the committee are satisfied that netarsudil-latanoprost and comparators have similar effectiveness. However, if the equal effectiveness case is not deemed sufficient for decision making, the EAG refers the read to Issue 4 in our critique of the company's technical engagement response and Section 4.2.8 of the EAG report for a full critique of the health state utility value evidence and assumptions.

Issue 5: Company's approach to selecting treatment acquisition costs

Following the first committee meeting, the EAG and company are agreed on the following points:

1) Netarsudil-latanoprost and comparators are most likely to be initiated in secondary care but will be prescribed routinely in primary care. Therefore, primary care prescribing costs should be considered for the assessment. Should the committee wish to consider secondary care prescribing, eMIT prices would apply and any confidential prices for comparators would also need consideration.

2) Given the high proportion of prescribing in primary care, confidential discounts, available through the CMU for any of the comparators are not relevant for this assessment.
3) A mix of branded and generic products will likely be prescribed in UK clinical practice.

Whilst the EAG and company agree that the market share data provided by the company accurately reflects current prescribing, there remains disagreement about the most appropriate unit costs for each treatment to apply in the economic model. The company preferred approach is to assign NHS indicative prices, obtained from the BNF, for branded products, but applying the drug tariff prices for the proportion of the market share that are prescribed as generics. The EAG prefers the use of drug tariff prices for all treatments. These prices more accurately capture the price paid to pharmacies for dispensing treatments in primary care and are in line with NICE's preferred hierarchy of costing sources which states "For drugs that are predominantly prescribed in primary care, prices should be based on the Drug Tariff". [1] The EAG, therefore, prefer to apply the drug tariff price from the BNF for all treatments in primary care. Company and EAG preferred treatment acquisition costs, by class of treatment, are compared in Table 1 below.

Table 1: Comparison of EAG and company preferred treatment acquisition costs

Treatment	Treatment class	Company preferred costs		EAG preferred costs	
		Cost per pack (£)	Treatment cost per cycle (with wastage)	Cost per pack (£)	Treatment cost per cycle (with wastage)
Roclanda 50micrograms/ml + 200micrograms/ml eye drops	Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]
Azarga 10mg/ml / 5mg/ml eye drops	Brinzolamide-Timolol	11.05	10.30	4.04	3.77
Brinzolamide 10mg/ml / Timolol 5mg/ml eye drops	Brinzolamide-Timolol	3.17	2.96	3.17	2.96
Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops 0.2ml unit dose preservative free	Dorzolamide-Timolol	17.86	17.86	17.86	17.86
Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops	Dorzolamide-Timolol	1.70	1.58	1.70	1.58
Cosopt 20mg/ml / 5mg/ml eye drops	Dorzolamide-Timolol	10.05	9.37	1.70	1.58
Cosopt 20mg/ml / 5mg/ml eye drops 0.2ml unit dose preservative free	Dorzolamide-Timolol	28.59	28.59	17.86	17.86
Cosopt iMulti 20mg/ml / 5mg/ml eye drops preservative free	Dorzolamide-Timolol	28.00	14.00	28.00	14.00
Eylamdo 20mg/ml / 5mg/ml eye drops	Dorzolamide-Timolol	8.13	7.58	8.13	7.58
Vizidor Duo 20mg/ml / 5mg/ml eye drops	Dorzolamide-Timolol	8.14	7.59	8.13	7.58
Latanoprost 50micrograms/ml / Timolol 5mg/ml eye drops	Latanoprost-Timolol	5.20	4.85	5.20	4.85
Fixapost 50micrograms/ml / 5mg/ml eye drops 0.2ml unit dose	Latanoprost-Timolol	13.49	13.49	13.49	13.49
Medox 50micrograms/ml / 5mg/ml eye drops	Latanoprost-Timolol	14.00	13.05	3.47	3.24
Xalacom eye drops	Latanoprost-Timolol	14.32	13.35	5.20	4.85

Treatment	Treatment class	Company preferred costs		EAG preferred costs	
		Cost per pack (£)	Treatment cost per cycle (with wastage)	Cost per pack (£)	Treatment cost per cycle (with wastage)
Taptiqom 15micrograms/ml / 5mg/ml eye drops 0.3ml unit dose	Tafluprost-Timolol	14.50	14.50	14.50	14.50
Bimatoprost 300micrograms/ml / Timolol 5mg/ml eye drops	Bimatoprost-Timolol	14.16	11.19	14.16	11.19
Eyzeetan 0.3mg/ml / 5mg/ml eye drops preservative free	Bimatoprost-Timolol	14.16	11.19	14.16	11.19
Ganfort 0.3mg/ml / 5mg/ml eye drops 0.4ml unit dose	Bimatoprost-Timolol	17.94	14.18	17.94	14.18
Ganfort 0.3mg/ml / 5mg/ml eye drops	Bimatoprost-Timolol	14.16	14.16	14.16	14.16
Travoprost 40micrograms/ml / Timolol 5mg/ml eye drops	Travoprost-Timolol	4.51	4.20	4.51	4.20
DuoTrav 40micrograms/ml / 5mg/ml eye drops	Travoprost-Timolol	13.95	13.01	4.51	4.20
Simbrinza 10mg/ml / 2mg/ml eye drops	Brinzolamide-Brimonidine	9.23	8.61	9.23	8.61
Combigan eye drops (priced by 3*5ml pack)	Brimonidine-Timolol	27.00	9.00	27.00	9.00
Combigan eye drops (priced by 1*5ml pack)	Brimonidine-Timolol	10.00	9.32	13.22	12.33

Key: EAG, external assessment group

Issue 6: Company's approach to costing adverse events

At technical-engagement model, the company further revised their approach to calculating adverse event unit costs. The revised approach involved calculating a weighted average of mild, moderate and severe adverse events from the MERCURY-3 trial (pooled across arms). Adverse events across all treatments were assumed to have the same weighting of mild, moderate and severe and the following unit costs were applied:

- Mild: £0,
- Moderate: EAG preferred unit costs (See Table 15 of EAG report)
- Severe: Company preferred unit costs from the company's original submission (See Table 15 of the EAG report).

The EAG notes that the company have attempted to account for the severity of adverse events within their unit cost calculations. The EAG accepts that many adverse events are mild and would not incur resource usage. However, the company's approach should not be interpreted as accounting for any differences in severity of adverse event across comparator arms of the model, because the weighted average cost is applied to the rate of all adverse events, regardless of severity. The EAG notes that incremental adverse event costs are broadly similar according to the company's revised approach and the EAG's preferred approach from technical engagement. The EAG considers the company's approach to be acceptable for decision making and notes that the impact of EAG vs. revised company preferred assumptions has little effect on incremental costs. See the EAG's critique provided at technical engagement (Issue 6) for further details.

Overall summary of the EAG's critique post technical engagement

There is one key remaining issue of disagreement between the company and EAG concerning the cost-comparison case for netarsudil-latanoprost vs. comparators. The EAG prefers the use of drug tariff prices, whereas the company prefers the use of drug tariff prices for generics, but NHS indicative prices for branded comparators. The impact of the company and EAG preferred base case are compared in Table 2 below.

Table 2 Company vs. EAG preferred cost-comparison assumptions

Treatment	Treatment class	Branded / generic	Market share	Overall Market share per class	Company preferred results		EAG preferred costs	
					Cost / patient / year	Inc. costs (Roclanda vs. comp.)	Cost / patient / year	Inc. costs (Roclanda vs. comp.)
Roclanda 50micrograms/ml + 200micrograms/ml eye drops	Netarsudil-latanoprost	Branded	N/A	N/A	£551.35		£551.35	
Azarga 10mg/ml / 5mg/ml eye drops	Brinzolamide-Timolol	Branded	1.86%	36%	£549.38	£1.97	£464.98	£86.37
Brinzolamide 10mg/ml / Timolol 5mg/ml eye drops	Brinzolamide-Timolol	Generic	3.29%	64%	£454.50	£96.85	£454.50	£96.85
Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops 0.2ml unit dose preservative free	Dorzolamide-Timolol	Generic	1.64%	6%	£650.74	-£99.39	£650.74	-£99.39
Dorzolamide 20mg/ml / Timolol 5mg/ml eye drops	Dorzolamide-Timolol	Branded	16.97%	58%	£440.56	£110.79	£440.56	£110.79
Cosopt 20mg/ml / 5mg/ml eye drops	Dorzolamide-Timolol	Branded	3.40%	12%	£541.10	£10.25	£440.56	£110.79
Cosopt 20mg/ml / 5mg/ml eye drops 0.2ml unit dose preservative free	Dorzolamide-Timolol	Branded	4.99%	17%	£789.31	-£237.96	£650.74	-£99.39
Cosopt iMulti 20mg/ml / 5mg/ml eye drops preservative free	Dorzolamide-Timolol	Branded	0.88%	3%	£600.89	-£49.54	£600.89	-£49.54
Eylamdo 20mg/ml / 5mg/ml eye drops	Dorzolamide-Timolol	Branded	0.93%	3%	£517.98	£33.37	£517.98	£33.37

Treatment	Treatment class	Branded / generic	Market share	Overall Market share per class	Company preferred results		EAG preferred costs	
					Cost / patient / year	Inc. costs (Roclanda vs. comp.)	Cost / patient / year	Inc. costs (Roclanda vs. comp.)
Vizidor Duo 20mg/ml / 5mg/ml eye drops	Dorzolamide-Timolol	Branded	0.42%	1%	£518.10	£33.25	£517.98	£33.37
Latanoprost 50micrograms/ml / Timolol 5mg/ml eye drops	Latanoprost-Timolol	Generic	5.32%	40%	£482.49	£68.86	£482.49	£68.86
Fixapost 50micrograms/ml / 5mg/ml eye drops 0.2ml unit dose	Latanoprost-Timolol	Branded	2.64%	20%	£594.09	-£42.74	£594.09	-£42.74
Medox 50micrograms/ml / 5mg/ml eye drops	Latanoprost-Timolol	Branded	0.00%	0%	£588.44	-£37.09	£461.66	£89.69
Xalacom eye drops	Latanoprost-Timolol	Branded	5.30%	40%	£592.30	-£40.95	£482.49	£68.86
Taptiqom 15micrograms/ml / 5mg/ml eye drops 0.3ml unit dose	Tafluprost-Timolol	Branded	1.09%	100%	£606.12	-£54.77	£606.12	-£54.77
Bimatoprost 300micrograms/ml / Timolol 5mg/ml eye drops	Bimatoprost-Timolol	Generic	4.12%	12%	£563.73	-£12.38	£563.73	-£12.38
Eyzeetan 0.3mg/ml / 5mg/ml eye drops preservative free	Bimatoprost-Timolol	Branded	0.83%	2%	£563.73	-£12.38	£563.73	-£12.38
Ganfort 0.3mg/ml / 5mg/ml eye drops 0.4ml unit dose	Bimatoprost-Timolol	Branded	6.13%	17%	£602.31	-£50.96	£602.31	-£50.96

Treatment	Treatment class	Branded / generic	Market share	Overall Market share per class	Company preferred results		EAG preferred costs	
					Cost / patient / year	Inc. costs (Roclanda vs. comp.)	Cost / patient / year	Inc. costs (Roclanda vs. comp.)
Ganfort 0.3mg/ml / 5mg/ml eye drops	Bimatoprost-Timolol	Branded	24.26%	69%	£602.08	-£50.73	£602.08	-£50.73
Travoprost 40micrograms/ml / Timolol 5mg/ml eye drops	Travoprost-Timolol	Generic	3.03%	42%	£476.89	£74.46	£476.89	£74.46
DuoTrav 40micrograms/ml / 5mg/ml eye drops	Travoprost-Timolol	Branded	4.23%	58%	£590.55	-£39.20	£476.89	£74.46
Simbrinza 10mg/ml / 2mg/ml eye drops	Brinzolamide-Brimonidine	Branded	6.67%	100%	£534.50	£16.85	£534.50	£16.85
Combigan eye drops (priced by 3*5ml pack)	Brimonidine-Timolol	Branded	0.07%	4%	£534.81	£16.54	£534.81	£16.54
Combigan eye drops (priced by 1*5ml pack)	Brimonidine-Timolol	Branded	1.93%	96%	£538.98	£12.37	£577.75	-£26.40

References

[1] NICE; "The Guidelines Manual," NICE, London, 2012.