For committee – contains ACIC information

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

Technology appraisal committee D [8 February 2024]

Chair: Megan John

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

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on glaucoma and intraocular pressure (IOP)

Causes

- Glaucoma is usually associated with increased pressure within the eye, known as IOP, caused either by too much aqueous humor produced or decreased drainage of this fluid. A build-up of too much pressure in the eye causes damage to the optic nerve.

Epidemiology

- Primary open-angle glaucoma (POAG) is the most common form in the UK, with estimates of about 2% of people aged ≥40 have POAG, and 10% of people ≥75 years.
- **Diagnosis**
- Estimated that 50% of people with POAG not have been diagnosed, because detection of POAG is often opportunistic and people may not be aware they have it.

Symptoms and prognosis

- Glaucoma causes progressive and irreversible visual impairment.

Patient and clinical perspectives*

Netarsudil-latanoprost provides innovative and complementary method of action

- Difficult to predict disease progression, which causes anxiety for people with glaucoma.
- Progressive irreversible loss of sight impacts substantially on the quality of life and requires carers to help with everyday activities.
- More treatment options are needed that can safely lower IOP and are effective even with lower starting pressures. Ideally with the potential to prevent and possibly reverse the biological changes seen in patients.
- A once-daily combination drop is easier to manage than multiple eye drops, multiple times a day.
- Given its unique and complementary properties to current medications, this technology offers additional potential to slow or stop glaucoma's irreparable damage to the optic nerve and vision.
- Red eye is a common side effect, but not usually uncomfortable and is reversible. Impact on prolonging sight years and QoL needs long-term studies.

* See appendix –Patient perspectives and Clinical perspectives

IOP, intraocular pressure; QoL, quality of life

Equality considerations

Potential equality issues raised at technical engagement stage

Ethnicity

- Glaucoma risk differs between ethnic groups with an increased burden of glaucoma in Afro-Caribbean populations with earlier onset and rapid progression.
- There is not sufficient evidence to support separate evaluations of the clinical effectiveness and cost-effectiveness of netarsudil-latanoprost for separate ethnic groups.

Disability

- The once-daily treatment may reduce inequalities by providing a simpler regime which may be better adhered to by vulnerable patients or their carers.
- Consideration should be given to bottle design to ensure less able patients can administer drops.
- Some additives such as preservatives can cause intolerance in patients with cornea damage.

Treatment pathway: open-angle glaucoma

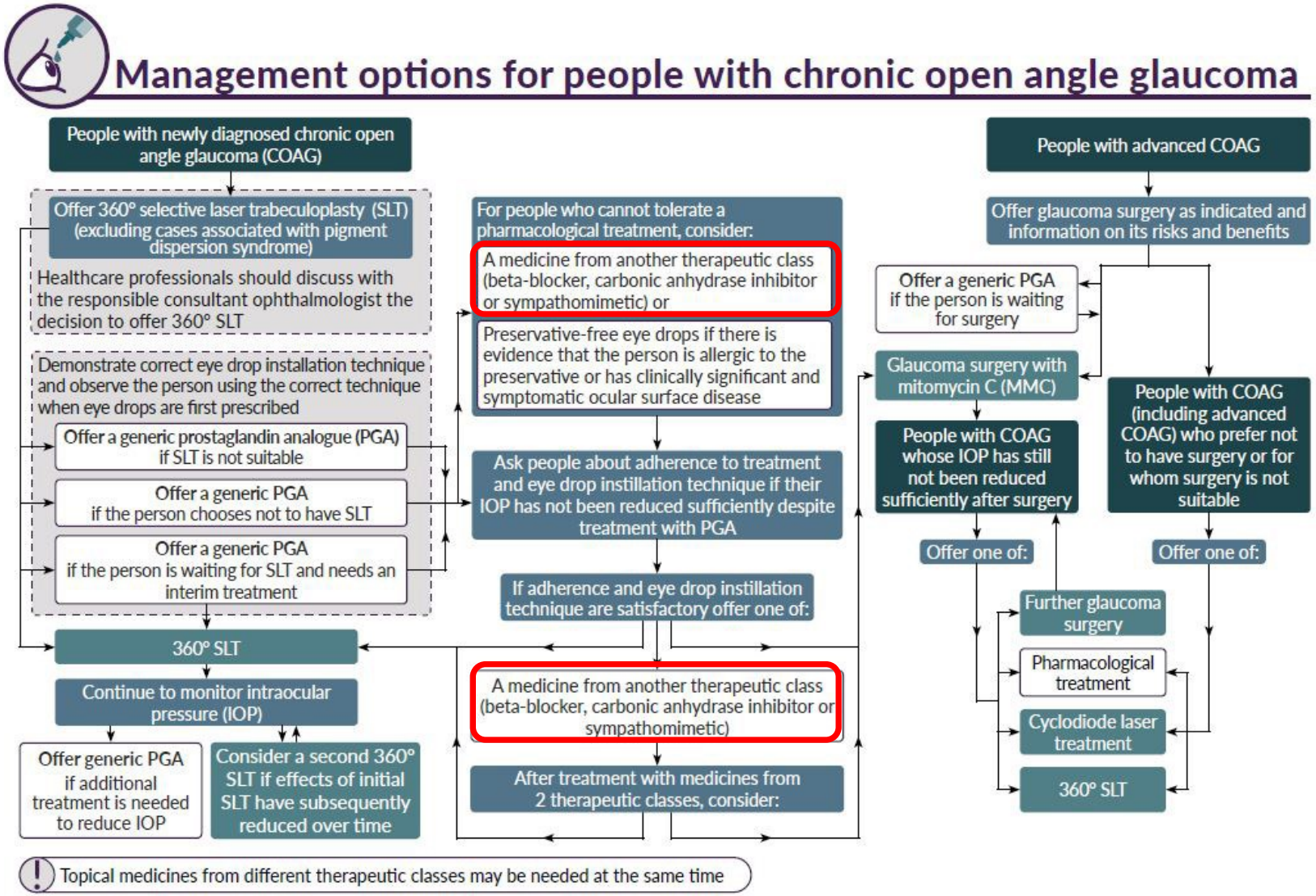

Figure adapted from NICE guidelines NG81: Glaucoma Diagnosis and Management

Management of OHT & POAG involves:

- topical medications (eye drops)
- selective laser trabeculoplasty (SLT)
- surgery (e.g. trabeculectomy)

Netarsudil-latanoprost would provide an alternative therapeutic option after primary therapy (highlighted in red).

Comparator treatments used at same point in the treatment pathway include:

- brinzolamide-timolol
- travoprost-timolol
- dorzolamide-timolol
- latanoprost-timolol
- tafluprost-timolol
- bimatoprost-timolol
- brimonidine-timolol
- brinzolamide-brimonidine

IOP, intraocular pressure; OHT, ocular hypertension; POAG, primary open-angle glaucoma COAG, chronic open-angle glaucoma; MMC, Mitomycin C; SLT, Selective laser trabeculoplasty; PGA, prostaglandin analogue

Netarsudil-latanoprost (Roclanda, Santen)

Marketing authorisation	• 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 • Granted via European Commission Decision Reliance Procedure on 8 January 2021
Description of technology	• 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, via different mechanisms of action.
Administration	• For ocular use only • Recommended dosage is one drop in the affected eye(s) once daily in the evening
Price	• List price for netarsudil-latanoprost is £14.00 per 2.5 ml bottle • Annual cost of treatment is £204.54 at list price (monthly total cost of £17.05)

IOP, intraocular pressure

Key issues

Issue	Resolved?	ICER impact
1: Non-systematic inclusion of monotherapy trials the network meta-analysis	No – for discussion	Unknown
2: Economic model structure does not capture disease progression	No – for discussion	Unknown
3: Assumption that those who discontinue treatment have the same intraocular pressure as those who remain on treatment	No – for discussion	Unknown
4: Approach to applying health state utility values creates uncertainty	No – for discussion	Unknown
5: Assumption of an average market share of branded and generic comparators within class	No – for discussion	Unknown
6: Assumption of secondary care resource use to manage mild and moderate adverse events	No – for discussion	Unknown

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Key clinical trial

	MERCURY 3
Design	Prospective, double-blind, randomised (1:1), multicentre, active-controlled, parallel-group safety and efficacy trial
Population	• Diagnosis of OAG or OHT in both eyes (OAG in one eye and OHT in the fellow eye was acceptable) • People with insufficiently controlled disease and/or considered in need for combination therapy by the investigators
Intervention	Netarsudil 0.02% and latanoprost 0.005% ophthalmic solution (once per day)
Comparator	Bimatoprost 0.03% and timolol maleate 0.5% ophthalmic solution (once per day)
Duration	6 months (first three months used to evaluate primary efficacy endpoint)
Primary outcome	Mean IOP (measured at 08:00, 10:00, and 16:00 hours at week 2, week 6, and month 3 study visits)
Key secondary outcomes	Mean diurnal IOP within a treatment group at each post-treatment visit (used in model)
Locations	68 participating secondary care outpatient sites in 11 countries (Austria, Belgium, Czechia, France, Germany, Hungary, Italy, Latvia, Poland, Spain, UK)

NICE

OAG, Open-angle glaucoma; OHT, Ocular hypertension; IOP, Intraocular pressure

MERCURY 3 trial results

Clinical non-inferiority of netarsudil-latanoprost relative to bimatoprost-timolol was demonstrated

- Primary outcome of MERCURY 3 is mean IOP (mmHg), measured at 0800, 1000 and 1600 hours at Week 2, Week 6 and Month 3.
- Clinical non-inferiority of netarsudil-latanoprost relative to bimatoprost-timolol 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.
- Clinical expert consulted by EAG suggests a difference of less than 2 mmHg is not clinically meaningful.

What is a clinically meaningful difference in IOP measured in mmHg?

See MERCURY 3 trial results (1)

CI, Confidence interval; IOP, Intraocular pressure; mmHg, Millimetres of mercury

Key issue 1: Non-systematic inclusion of trials in the NMA*

Background

- Reliability of the company's clinical effectiveness evaluation is uncertain because of the non-systematic inclusion of monotherapies used to connect the network in the company's NMA.
- Due to large number of FDC comparators, robust NMA is essential for understanding relative effectiveness.

Company

- A pragmatic approach was taken for the original NMA using monotherapy studies to connect the network. In response to the EAG's concerns, alternative network using 2 additional monotherapy studies proposed.
- New base case analysis (random effects model) and sensitivity analysis (fixed effects model) were provided. Treatment effect was comparable between these 2 analyses, with both indicating no difference in effect between different treatment strategies, largely aligning with original NMA.

EAG comments

- EAG hoped that updated evidence would follow general principles of systematic reviews (as outlined in NICE DSU TSD1), but there remains a lack of transparency regarding why the additional studies were chosen and why netarsudil was included as an additional comparator.
- Any non-systematic selection of studies and comparators means that results could be prone to bias.
- EAG not satisfied that all FDCs have the same effect and suggest that results be interpreted with caution.

Do the company's new NMAs sufficiently address concerns about potential risk of bias?

* See NMA methodology

* See NMA network diagram

NMA, network meta-analysis; FDC, fixed-dose combination; DSU, decision support unit; TSD1, technical support document 1

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Key issue 2: Economic model structure does not capture disease progression (1)

Background

- Company's original model structure not appropriate for lifetime horizon assessment: does not capture costs and QALY benefits of slowing conversion from OHT to glaucoma, or glaucoma disease progression.
- Model allows transitions between any of the 3 non-death health states, so implicitly assumes that vision loss due to glaucoma is reversible.
- IOP is the only modifiable risk factor for glaucoma, but it is a surrogate marker for symptomatic disease.
- Alternative health states could have been defined by mild/moderate/severe disease, for example.

Company

- In response to EAG concerns, proposes an alternative analysis based on a shorter time horizon (using time on treatment, base case: 12 months) and excluding the impacts of treatment discontinuation.
- This approach reduces uncertainty and dependence on estimates and assumptions for longer-term efficacy, QoL, and the treatment pathway for discontinuing patients (where data is limited).
- All patients now remain on treatment for full time horizon instead of moving to a 'second line' weighted basket comparator (reduces risk of ICER being driven more by comparator data than treatment arm data).
- Sensitivity analyses demonstrate limited impact of changes in the time horizon.

IOP, intraocular pressure; OHT, ocular hypertension, QoL, quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Key issue 2: Economic model structure does not capture disease progression (2)

EAG comments

- EAG position remains unchanged concerning the appropriateness of the economic model structure.
- To conduct a robust assessment of cost-effectiveness a lifetime time horizon is required, using an economic model that captures conversion from OHT to glaucoma and progression of glaucoma over time.
- A more appropriate model structure could have used Markov states defined by OHT and COAG stage.
- Disagree with company that OHT and glaucoma are not suitable for a life-time horizon model.
- Only scenario where a lifetime model might not be required is if evidence that interventions and all comparators provide equivalent outcomes.
- Given lack of robust evidence from the NMA, EAG remains unconvinced that an assumption of equivalent effectiveness compared to any comparator except bimatoprost-timolol (MERCURY 3) can be justified.

Clinical expert comment:

- Model provided by the company does not adequately study the long-term costs and QALYs of IOP changes, only short-term changes.
- There are several published economic models (EAG report Table 10) that could be used to construct an appropriate economic model.

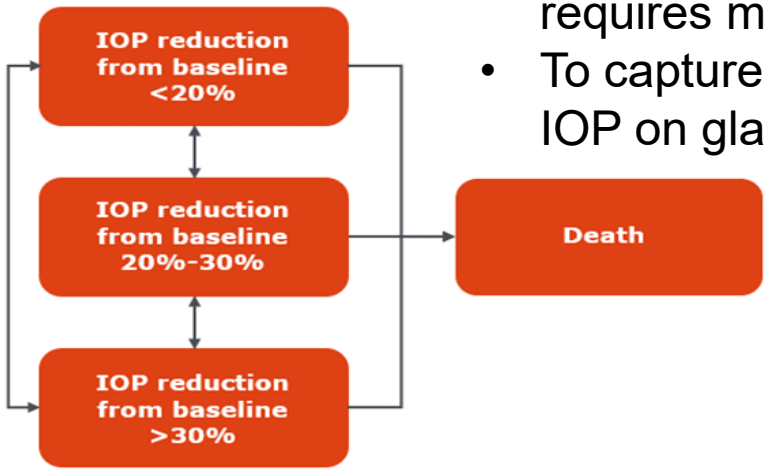
IOP, intraocular pressure; OHT, ocular hypertension; COAG, chronic open-angle glaucoma; NMA, network meta-analysis; QALY, quality-adjusted life year;

Key issue 2: Economic model structure does not capture disease progression (3)

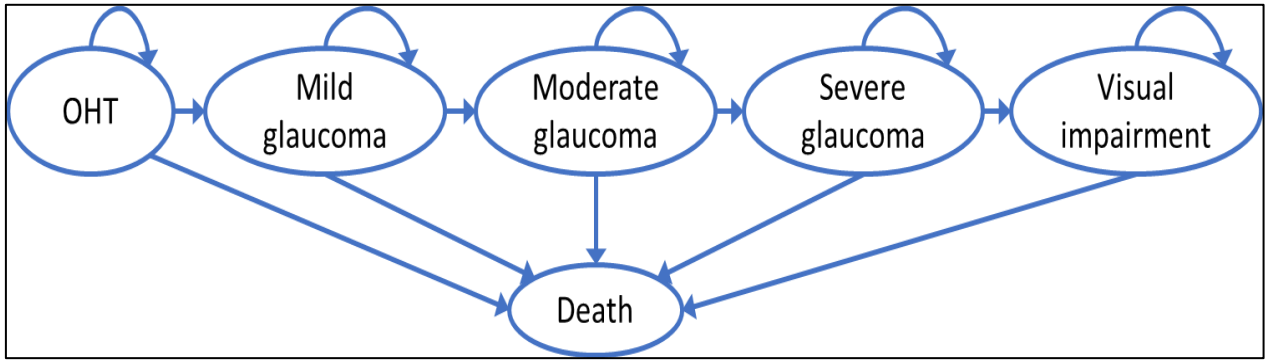
EAG comment

- Glaucoma 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.

Company's model structure (IOP health states):



EAG suggested model structure (e.g. COAG stage health states):



COAG stage	Mean defect score
No COAG	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	-20.01 or worse

Is the company's model appropriate for assessing full costs and benefits of the technology?

IOP, intraocular pressure; OHT, ocular hypertension; COAG, chronic open-angle glaucoma

See Company's model overview

Key issue 3: Model assumption: IOP on/off treatment

Background

- Data provided at clarification shows that patients who have discontinued a treatment have significantly higher IOP than those who remain on treatment.
- But company's original model assumes that patients who discontinue treatment have the same IOP as those who remain on treatment, thus the QALY losses from increases in IOP due to discontinuing treatment may not be adequately captured.

Company

- Company considers that its revised approach to modelling a time horizon based on time on treatment (12 months) and excluding all effects of treatment discontinuation (as detailed in key issue 2) resolves this issue.

EAG comments

- Company 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.
- This approach retains all limitations of an inappropriate model structure, and further increases potential for bias by removing future lines of treatment over time based on disease stage.

Is it appropriate to disregard the impacts of treatment discontinuation and subsequent lines of treatment from the model?

IOP, intraocular pressure; QALY, quality-adjusted life years; QoL, quality of life

Key issue 4: Approach to health state utility values creates uncertainty (1)

Background

- 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.
- In the company's original model, higher IOP percentage reductions are associated with higher utility weights. But EAG considers IOP level is not directly associated with variations in quality of life.
- This approach to applying health state utility values creates uncertainty because data provided by the company at clarification shows no clear relation between IOP reduction and QoL.

Company

- In response to the EAG's concerns, company did utility value scenario analysis by applying SF-6D tariff to the SF-36 data of MERCURY-3 using the appropriate algorithm, avoiding the need for mapping to EQ-5D.
- Comparing the SF-6D to EQ-5D utility values, the trend of increasing QoL with increasing reduction in IOP is maintained (suggests that the EQ-5D utility values may be conservative).
- Company retains EQ-5D utility values for their base case as it is better aligned to the NICE reference case.

IOP, intraocular pressure; EQ-5D, EuroQol- 5 Dimension Questionnaire; SF-6D – Short-Form Six-Dimension Questionnaire; QoL, quality of life

Key issue 4: Approach to health state utility values creates uncertainty (2)

EAG comments

- EAG note that SF-6D utility values in the model yield similar overall results to the base case EQ-5D utilities.
- But EAG consider that any differences in short term utility associated with changes in IOP do not reflect the impact on utility of glaucoma disease progression.
- 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.
- Beyond the short time horizon (one year), the SF-6D scenario is of limited value due to overall concerns with the model structure (as detailed in key issue 2).

Clinical expert comment

- The company's approach does not take into account the important fact of disease progression, resulting in over-estimation of long term QALYs.

If committee accepts company's model, are EQ-5D or SF-6D utility values preferred for the base case? If new model required, are there alternative sources of utility values that would be more appropriate?

See Alternative health state utility values

IOP, intraocular pressure; EQ-5D, EuroQol- 5 Dimension Questionnaire; SF-6D, Short-Form Six-Dimension Questionnaire; QALY, quality adjusted life year

Key issue 5: Assumption of an average market share of branded and generic comparators within class (1)

Background

- Each fixed-dose combination comparator treatment acquisition cost is calculated as a weighted average cost per cycle, weighted according to market share for branded and generic alternatives.
- Company assumes an average market share of branded (using NHS indicative prices) and generic (using drug tariff prices) products within class, prescribed in primary care.
- EAG prefers drug tariff prices for primary care or eMIT price for secondary care prescribing (if appropriate).

Company

- Weighting of branded and generic alternatives reflects real-world practice, where doctors will prescribe brand names due to patient preferences and brand loyalty.
- Market share data is based on UK sales December 2015 to December 2022. These values are extrapolated forward at the same trajectory for 2023 to 2028 (time horizon of budget impact model).
- Using generic prices only would be unrepresentative of the UK market.

Clinical expert comment

- Presently, clinicians in secondary care or specialist clinics initiate the prescription during consultations, and afterward, general practitioners continue to prescribe it.

eMIT, electronic market information tool

Key issue 5: Assumption of an average market share of branded and generic comparators within class (2)

EAG comments

- 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.
- If committee agrees that prescriptions for glaucoma are mostly issued in primary care, then drug tariff price are appropriate because they more accurately capture the price paid to pharmacies for dispensing treatments in primary care and are in line with NICEs preferred hierarchy of costing sources .
- While branded prescribing should continue for people already on treatment, generic substitution for all new prescriptions should be considered.
- Unlikely someone starting new line of treatment will have brand loyalty for treatment they haven't yet used.

Technical team comment

- The technical team note that EAG and company both agree that FDC comparators are usually initiated in secondary care but managed and prescribed routinely in primary care (based on market share data, clinical expert opinion). But this may differ across the country.
- Should it transpire that treatment is mostly prescribed in secondary care, then eMIT prices would be more appropriate (and EAG's confidential cPAS price analysis would be relevant).

Are the majority of prescriptions for glaucoma issued within primary care?
If so, are NHS indicative prices or drug tariff prices more appropriate?

FDC, fixed-dose combination; cPAS, confidential patient access scheme; eMIT, electronic market information tool

Key issue 6: Assumption of secondary care resource use to manage mild and moderate adverse events (1)

Background

- The company's original economic model included adverse events (AEs) of any severity, occurring in at least 5% of patients in either the netarsudil-latanoprost or bimatoprost-timolol arm of the MERCURY 3 trial.
- Per-cycle probability of AEs 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 routine monitoring.
- Company assumes a more intensive use of secondary care resources to manage mild and moderate adverse events than would be expected in UK clinical practice.

Company

- In response to EAG's concerns, company adjusted resource use to reflect severity as reported in the MERCURY-3 trial.
- AEs of mild severity assumed to not require any resource use and were excluded.
- For moderate AEs, assumed that resource use was in line with EAG's preferred assumptions.
- For severe AEs, assumed that resource use is in line with company's original submission.

Key issue 6: Assumption of secondary care resource use to manage mild and moderate adverse events (2)

EAG comments

- EAG's clinical expert provided an alternative set of assumptions regarding resource use for each AE, based on an adverse event assumed to be of moderate severity (Grade II on average).
- Proportion receiving resource is intended to reflect proportion of patients experiencing each event that would require an additional ophthalmology consultation outside of the normal scheduled routine monitoring.
- Given that there are no severe AEs reported in MERCURY 3 trial, EAG retains its original preference for less intensive resource use for managing adverse events in the model.
- EAG 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, it remains concerned that there is significant residual uncertainty for the AE management cost of the remaining comparators.

Clinical expert comment

- There is an overestimation of the resources that would be used in clinical practice in the UK. So there is a bias in the cost-effectiveness of treatments with higher adverse events.

Are the company's revised resource costs for AEs appropriate?

AE, adverse event

Company updated base case results: deterministic, incremental

Deterministic base case results: fully incremental, treatments ranked in ascending order of cost

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Net monetary benefit (NMB)*	EAG calculated NMB rank
Brinzolamide-timolol	[redacted]	[redacted]	-	-	-	[redacted]	[redacted]
Dorzolamide-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]	[redacted]
Brinzolamide-brimonidine	[redacted]	[redacted]	[redacted]	[redacted]	51,063	[redacted]	[redacted]
Latanoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]	[redacted]
Travoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]	[redacted]
Brimonidine-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]	[redacted]
Tafluprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]	[redacted]
Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]	[redacted]
Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]	[redacted]

* Threshold equal to £30,000 for NMB calculation.

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

Company updated base case results: deterministic, pairwise

Deterministic base case results: pairwise comparisons – Netarsudil-latanoprost vs. comparators

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Net monetary benefit (NMB)*
Netarsudil-latanoprost	[redacted]	[redacted]	-	-		[redacted]
Brinzolamide-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Travoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	£16,305	[redacted]
Dorzolamide-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Latanoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Tafluprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	£2,416	[redacted]
Brimonidine-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
Brinzolamide-brimonidine	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

* Threshold equal to £30,000 for NMB calculation.

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QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

Company updated base case results: probabilistic

Fully incremental probabilistic base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Brinzolamide-timolol	[redacted]	[redacted]	[redacted]	[redacted]	-
Dorzolamide-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Brinzolamide-brimonidine	[redacted]	[redacted]	[redacted]	[redacted]	50,810
Latanoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Travoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Brimonidine-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Tafluprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Netarsudil-latanoprost	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Bimatoprost-timolol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

- 10,000 iterations were run for the base case analysis to ensure stability in results.
- Mean probabilistic results are similar to the base case for all comparators.

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

EAG base case results

- 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.

- 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.

IOP, intraocular pressure; QALY, quality-adjusted life year

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Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.
- **No managed access proposal was received from the company for this evaluation.**

Severity modifier

- No proposal for a severity modifier was received from the company.

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Issue	Resolved?	ICER impact
1: Non-systematic inclusion of monotherapy trials the network meta-analysis	No – for discussion	Unknown
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Supplementary appendix

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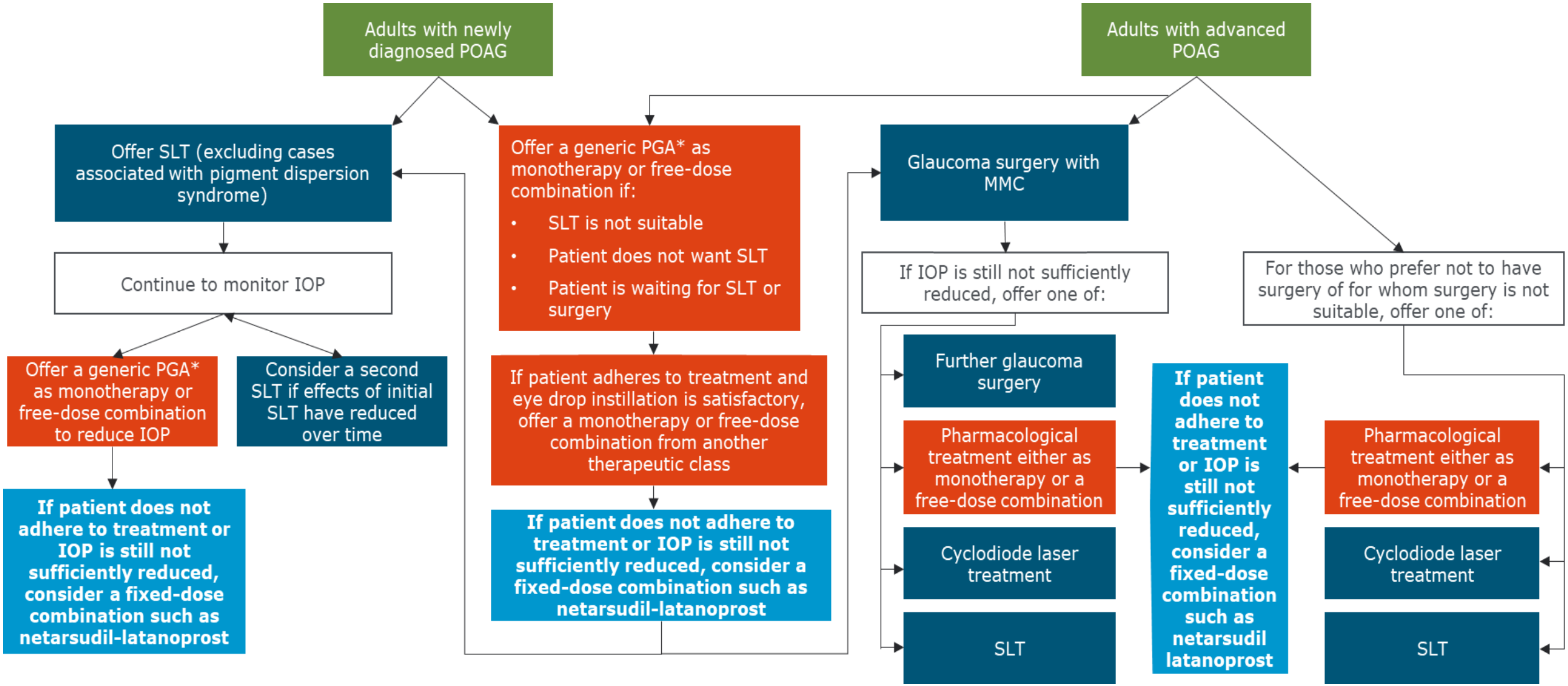
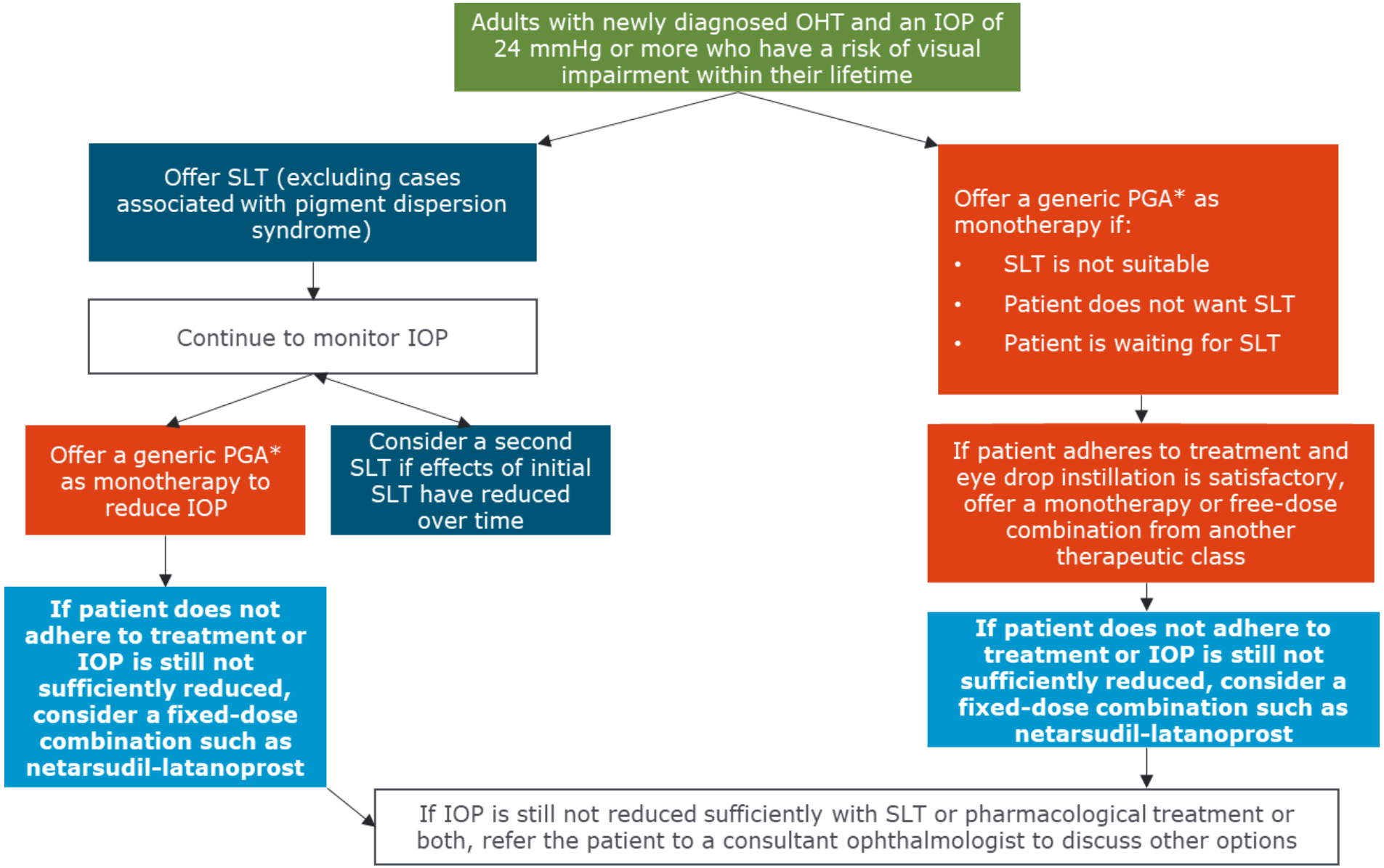
Company's proposed treatment pathway: POAG



IOP, intraocular pressure; POAG, primary open-angle glaucoma; MMC, Mitomycin C; SLT, Selective laser trabeculoplasty; PGA, prostaglandin analogue

Company's proposed treatment pathway: OHT



OHT, ocular hypertension; IOP, intraocular pressure; POAG, primary open-angle glaucoma; MMC, Mitomycin C; SLT, Selective laser trabeculoplasty

Patient perspectives

Glaucoma associated with anxiety and reduced quality of life

Submission from Glaucoma UK

- People feel powerless: no lifestyle factors are proven to improve prognosis
- Difficult to predict disease progression, which causes anxiety. Must inform DVLA if glaucoma in both eyes, causing additional uncertainty regarding loss of independence and mobility
- Laser treatment usually only works for a few years and must be repeated.
- Treatment can be stressful because of delayed appointments, seeing lots of different clinicians and experiencing long waits in clinics. Most people with glaucoma are older, exacerbating these challenges
- Eye drops can cause adverse reactions such as itchy/sore eyes. Droppers can be difficult to use correctly, especially for people with dexterity issues
- Progressive irreversible loss of sight impacts substantially on quality of life, and carers may have to help with everyday activities

"There is no cure for glaucoma. Once you have it, you are in for a rollercoaster of operations and lifelong use of drops."

"A once-daily combination drop is easier to manage than multiple eye drops, multiple times a day."

Clinical perspectives

Submissions from Moorfields Eye Hospital & Liverpool University Hospital Foundation Trust

- Primary aim of treatment is to lower IOP to help prevent progression of OHT to OAG. Or, in the case of OAG, to halt or reduce the rate of visual loss.
- The technology provides innovative ways to lower IOP and slow glaucoma progression. But studies have not reported quantifiable data on disease progression, such as visual field defects or neuroretinal rim thinning. Any impact on increasing sight years and improving QoL will need to be shown in longer-term studies.
- In clinical practice, some eye drops are preferred over others due to differences in side effect profiles and clinician experience. For patients, some bottles may be harder or easier to use than others.
- More treatment options that can safely lower IOP are required, particularly drops that are effective even with lower starting pressures, and which are not difficult to adhere to (e.g. required multiple times a day)

"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"

"Red eye is a common side effect, but not usually uncomfortable and is reversible. While intolerable for some, others will be very willing to have a red eye to prevent vision loss or avoid surgery"

Link to Patient and clinical perspectives*

OAG, Open-angle glaucoma; OHT, Ocular hypertension; IOP, Intraocular pressure; QoL, quality of life

Decision problem (1)

	Final scope	Company
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
Intervention	Netarsudil-latanoprost (Roclanda®)	Netarsudil-latanoprost (Roclanda®)

Comparators	• 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).

Decision problem (2)

	Final scope	Company
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

EAG comments:

- 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.

MERCURY 3 trial results (1)

Mean IOP (mmHg) at 0800, 1000 and 1600 hours at Week 2, Week 6 and Month 3

	Net-lat (N=218)	Bim-tim (N=212)	Difference from bim-tim
Week 2 (day 15), 08:00 hours			
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			
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			
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			
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			
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			
LS mean (p-value)	[redacted]	[redacted]	-0.08 (0.7613)
SE [95% 2-sided CI]	[redacted]	[redacted]	0.28 [-0.63, 0.46]

NICE

CI, Confidence interval; IOP, Intraocular pressure; LS, Least square; SE, Standard error; mmHg, Millimetres of mercury; **p-value <0.01

MERCURY 3 trial results (2)

	Net-lat (N=218)	Bim-tim (N=212)	Difference from bim-tim
Month 3 (day 90), 08:00 hours			
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			
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			
LS mean (p-value)	[redacted]	[redacted]	0.19 (0.5126)
SE [95% 2-sided CI]	[redacted]	[redacted]	0.29 [-0.38, 0.76]

CI, Confidence interval; IOP, Intraocular pressure; LS, Least square; SE, Standard error; mmHg, Millimetres of mercury; *p-value <0.05

NMA methodology

A connected network was created using monotherapy studies

- Company's original NMA comprised 2 separate networks of trials: one involving netarsudil-latanoprost included 5 treatments and 3 trials, the second included 7 treatments and 6 trials.
- EAG advised company to consider including monotherapy trials to bridge the disconnected networks.
- Company formed a bridge using MERCURY 1, MERCURY 2 and one other trial (DuBiner et al., 2001).
- EAG cautioned the process to identify these trials was not systematic.
- In response, at technical engagement stage, company reconsidered the monotherapy studies that were extracted in the original SLR and conducted a new NMA as sensitivity analysis.
- This alternative NMA was not reliant on a single connection via latanoprost, being formed with an additional study from new targeted database search (Fechtner et al. [2004]).
- All three arms of the MERCURY 1 and MERCURY 2 studies were now also included (previously, only netarsudil-latanoprost and latanoprost arms were considered), with the netarsudil arm providing an additional loop via this monotherapy.

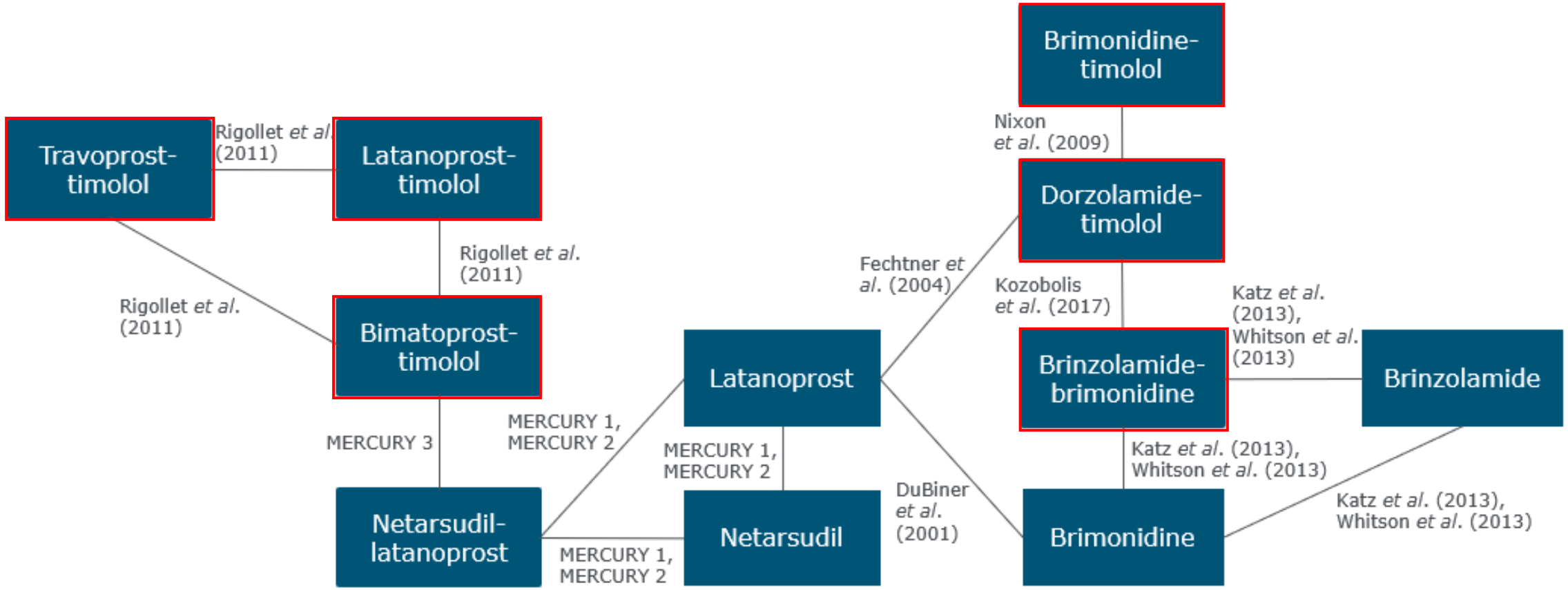
Key issue 1: Non-systematic inclusion of trials in the NM...

NMA, network meta-analysis; SLR, systematic literature review

NMA network diagram

Company's updated NMA with 3 additional studies forming network bridge

Red box indicates FDC comparators of interest



FDC, fixed dose combination

NMA results: Company base case (random effects model)

Forest plot - percentage change in diurnal IOP from baseline

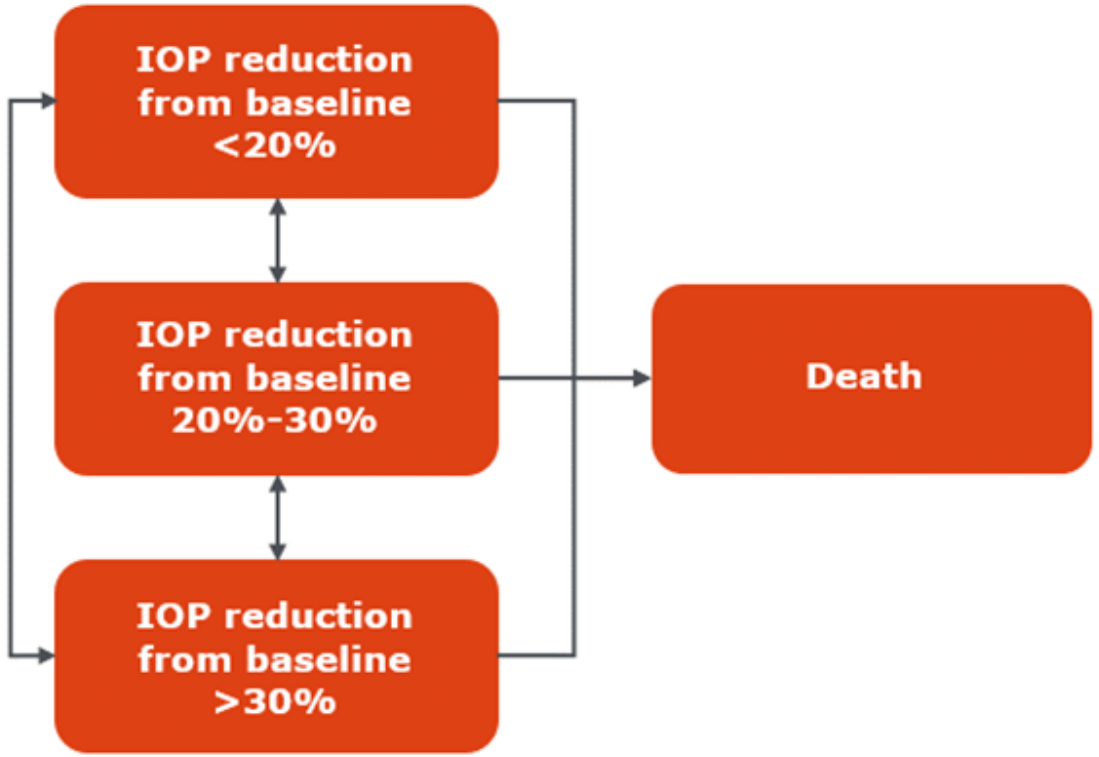
- Patients treated with netarsudil-latanoprost had a greater percentage change in diurnal IOP from baseline compared to netarsudil, dorzolamide-timolol, brinzolamide, brinzolamide-brimonidine, brimonidine, latanoprost and travoprost-timolol (treatment effect [95% CrI]: [redacted], respectively).
- However, the treatment effects for the comparison of netarsudil-latanoprost with all treatments are close to zero, indicating that these treatments have similar efficacy.

Adverse events from the MERCURY-3 trial

	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]

Company's model overview

Company's model structure



Factor	Chosen values
Time horizon	Lifetime (33 years)
Cycle length	1 month (30.44 days)
Discount rate for costs/ outcomes	3.5%
Perspective	UK NHS and PSS
Half-cycle correction	Yes
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.
Source of utilities	MERCURY 3 SF-36 data

Key issue 2: Economic model structure does not capture di...

IOP, intraocular pressure; PSS, Personal Social Services; SF-36, Short Form 36; ITC, indirect treatment comparison; SLR, systematic literature review; FDC, fixed-dose combination

Alternative health state utility values

Health state utility values from the MERCURY 3 trial: EQ-5D compared with SF-6D

Health state	EQ-5D utility value (standard error) – from company submission	SF-6D utility value (Standard error) – new sensitivity analysis
<20% reduction in IOP	[redacted]	[redacted]
20% - 30% reduction in IOP	[redacted]	[redacted]
>30% reduction in IOP	[redacted]	[redacted]

- 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

Key issue 4: Approach to health state utility values crea...

IOP, intraocular pressure; EQ-5D, EuroQol- 5 Dimension Questionnaire; SF-6D – Short-Form Six-Dimension Questionnaire

Company deterministic scenario analysis (1)

Company scenario analyses (deterministic)

Scenario	Technologies	Deterministic					
		Total costs (£)	Total QALYs (£)	Incremental costs (£)	Incremental QALYs	ICER (£) versus incremental QALYs	NMB (£) versus lowest total cost
5-year time horizon	Brin-tim	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
	Dorz-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brin-brim	[redacted]	[redacted]	[redacted]	[redacted]	77,487	[redacted]
	Lat-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Trav-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brim-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Taflu-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Net-lat	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Bim-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit

Company deterministic scenario analysis (2)

Company scenario analyses (deterministic)

Scenario	Technologies	Deterministic					
		Total costs (£)	Total QALYs (£)	Incremental costs (£)	Incremental QALYs	ICER (£) versus incremental QALYs	NMB (£) versus lowest total cost
2-year time horizon	Brin-tim	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
	Dorz-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brin-brim	[redacted]	[redacted]	[redacted]	[redacted]	63,882	[redacted]
	Lat-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Trav-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brim-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Taflu-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Net-lat	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Bim-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit

Company deterministic scenario analysis (3)

Company scenario analyses (deterministic)

Scenario	Technologies	Deterministic					
		Total costs (£)	Total QALYs (£)	Incremental costs (£)	Incremental QALYs	ICER (£) versus incremental QALYs	NMB (£) versus lowest total cost
SLT and trabeculectomy concomitant treatment costs included	Brin-tim	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
	Dorz-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brin-brim	[redacted]	[redacted]	[redacted]	[redacted]	49,767	[redacted]
	Lat-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brim-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Trav-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Taflu-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Net-lat	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Bim-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit

Company deterministic scenario analysis (4)

Company scenario analyses (deterministic)

Scenario	Technologies	Deterministic					
		Total costs (£)	Total QALYs (£)	Incremental costs (£)	Incremental QALYs	ICER (£) versus incremental QALYs	NMB (£) versus lowest total cost
All TEAEs modelled as severe	Brin-tim	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
	Brin-brim	[redacted]	[redacted]	[redacted]	[redacted]	37,482	[redacted]
	Dorz-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brim-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Lat-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Bim-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Tra-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Taflu-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Net-lat	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit

Company deterministic scenario analysis (5)

Company scenario analyses (deterministic)

Scenario	Technologies	Deterministic					
		Total costs (£)	Total QALYs (£)	Incremental costs (£)	Incremental QALYs	ICER (£) versus incremental QALYs	NMB (£) versus lowest total cost
NMA sensitivity analysis – random effects analysis	Brin-tim	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
	Dorz-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brin-brim	[redacted]	[redacted]	[redacted]	[redacted]	18,979	[redacted]
	Lat-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Trav-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brim-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Taflu-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Net-lat	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Bim-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit

Company deterministic scenario analysis (6)

Company scenario analyses (deterministic)

Scenario	Technologies	Deterministic					
		Total costs (£)	Total QALYs (£)	Incremental costs (£)	Incremental QALYs	ICER (£) versus incremental QALYs	NMB (£) versus lowest total cost
NMA sensitivity analysis – fixed effect analysis	Brin-tim	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
	Dorz-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brin-brim	[redacted]	[redacted]	[redacted]	[redacted]	21,049	[redacted]
	Lat-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Trav-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brim-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Taflu-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Net-lat	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Bim-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit

Company deterministic scenario analysis (7)

Company scenario analyses (deterministic)

Scenario	Technologies	Deterministic					
		Total costs (£)	Total QALYs (£)	Incremental costs (£)	Incremental QALYs	ICER (£) versus incremental QALYs	NMB (£) versus lowest total cost
SF-6D HSUVs	Brin-tim	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
	Dorz-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brinbrim	[redacted]	[redacted]	[redacted]	[redacted]	46,992	[redacted]
	Lat-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Trav-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Brim-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Taflu-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Net-lat	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]
	Bim-tim	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit