NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Clostridium botulinum neurotoxin type A for treating chronic sialorrhoea [ID1150]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Clostridium botulinum neurotoxin type A for treating chronic sialorrhoea [ID1150]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from **Merz Pharma**

2. **Company response to NICE's request for clarification**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Parkinsons UK
   b. Association of British Neurologists

4. **Expert personal perspectives** from:
   a. Professor K Ray-Chaudhuri, Clinical Expert, nominated by Merz Pharma
   b. Dr Tabish Saifee, Clinical Expert, nominated by Association of British Neurologists- *endorsing statement from ABN*

5. **Evidence Review Group report** prepared by School of Health and Related Research (ScHARR)

6. **Evidence Review Group – factual accuracy check**

7. **Technical engagement response** from **Merz Pharma**

8. **Technical engagement response from consultees and commentators:**
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9. **ERG addendum (post PAS)**

10. **Final Technical Report**

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Clostridium botulinum toxin A (Xeomin®) for treating chronic sialorrhoea [ID1150]

Document B

Company evidence submission

Merz Pharma UK Ltd

February 2019

File name	Version	Contains confidential information	Date
ID1150_Xeomin_Document B [ACIC]	1.0	Yes	8th February 2019

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Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) 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 150 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 guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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

B.1.1 Decision problem

This submission covers the full anticipated marketing authorisation for clostridium botulinum neurotoxin type A (hereafter referred to as Xeomin) as a treatment for adult patients with chronic sialorrhoea (excessive drooling).

The decision problem addressed within this submission aligns with the NICE final scope for this appraisal as described 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 chronic sialorrhoea.	Adults with chronic sialorrhoea.	N/A – in line with the NICE final scope.
Intervention	Clostridium botulinum neurotoxin type A.	Xeomin (botulinumtoxin type A).	N/A – in line with the NICE final scope.
Comparator(s)	• Anticholinergic drugs such as glycopyrronium bromide For people where anticholinergic drugs are unsuitable: • Established clinical management without clostridium botulinum toxin A.	This submission compares Xeomin with the following relevant comparators: • Glycopyrronium bromide For people in whom anticholinergic drugs are unsuitable: • Standard of care (SoC; basic non-pharmacological management)	Chronic sialorrhoea is heavily untreated. A large proportion of patients do not receive active therapy, and their sialorrhoea is instead managed with basic non-pharmacological management (SoC), which may include practical aids, such as bibs, as well as speech, language and occupational therapy. For patients who do receive active therapy, anticholinergic therapies such as glycopyrronium bromide may be tried. Where anticholinergic therapies are unsuitable, patients will receive SoC. Feedback from UK clinical experts experienced in the clinical management of sialorrhoea indicated that glycopyrronium bromide is one of the most routinely used anticholinergic therapies. Some patients may be treated with other anticholinergic

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			therapies such as transdermal hyoscine hydrobromide or atropine sulfate; as such, scenario analyses have been performed versus these comparators.[1]
Outcomes	The outcome measures to be considered include: • Unstimulated salivary flow rate • Response rates • Adverse effects of treatment • Health-related quality of life	The following outcomes have been included within this submission: • Unstimulated salivary flow rate (uSFR) • Drooling Severity and Frequency Scale (DSFS) • Modified Radboud Oral Motor Inventory in Parkinson's Disease (mROMP) • Patient's Global Impression of Change Scale (GICS) • Carers' GICS • Response rates (GICS entry ≥1) • Adverse effects of treatment • Health-related quality of life o EQ-5D-3L	N/A – 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 cost-effectiveness of Xeomin versus the relevant comparators has been expressed in terms of incremental cost per quality-adjusted life year • A time horizon of 10 years has been chosen for the base case, which was considered an appropriate duration over which to fully capture the costs and benefits of Xeomin versus the relevant comparators without introducing unnecessary extrapolation-related uncertainties. Scenario analyses exploring alternative time horizons, including a lifetime time horizon, were also	N/A – in line with the NICE final scope.

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		conducted. • All costs have been considered from an NHS and Personal Social Services perspective.	
Other considerations	If the evidence allows the following subgroups will be considered. These include: • adults with dysphagia (difficulty swallowing) • underlying condition causing sialorrhoea Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	No subgroups have been considered for the economic analysis.	No data are available for Xeomin or the relevant comparators in the subgroup identified as adults with dysphagia (difficulty swallowing); in addition, this subgroup is not considered to be clinically relevant given patients with sialorrhoea are not typically defined as either having dysphagia or not in clinical practice. In terms of the underlying condition causing sialorrhoea, the potential for an economic comparison was not feasible given the lack of subgroup data available for the relevant comparators. It should be noted that the mechanism of action of Xeomin is such that the treatment effect is independent of the aetiology of the sialorrhoea. Therefore, and as implicitly recognised by the FDA (and soon to be EMA) in their provision of a broader licence for Xeomin regardless of aetiology,[2] there is no reason to suggest that the efficacy of Xeomin observed within the SIAXI trial would not translate to patients suffering from sialorrhoea due to conditions outside of those suffered by the patients within the SIAXI trial.

Abbreviations: GICS: Patient's Global Impression of Change Scale**;** mROMP: Modified Radboud Oral Motor Inventory in Parkinson's Disease; N/A: not applicable
Source: NICE Final Scope ID1150.[3]

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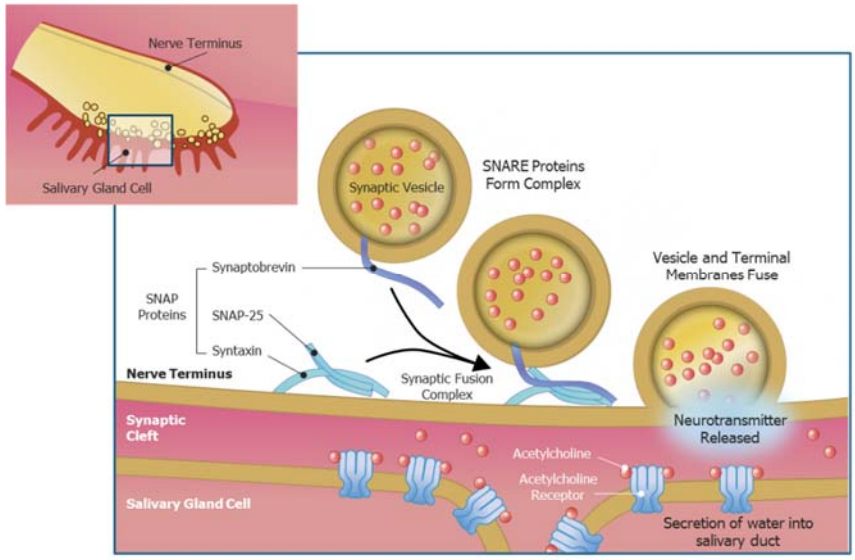
B.1.2 Description of the technology being appraised

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements of Xeomin in the treatment of chronic sialorrhoea is presented in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Xeomin® (botulinumtoxin type A).
Mechanism of action	Xeomin is a Botulinum neurotoxin type A, one of ~7 serotypes of Botulinum toxin, a neurotoxic protein produced by *Clostridium sp.* It is delivered as injections into the submandibular and parotid glands to treat chronic sialorrhoea by slowing the production of saliva. Saliva is produced by the acinar cells of the salivary glands and secreted into the oral cavity via a system of ducts.[4] The majority of the saliva in the oral cavity is secreted by three pairs of salivary glands: the parotid, sublingual and submandibular glands.[4, 5] Fluid secretion by these salivary glands is partially controlled by the surrounding nerves. Stimulated parasympathetic nerves release acetylcholine at the neuroglandular junction, which activates muscarinic acetylcholine receptors on the acinar cells, simulating the release of Ca^{2+} into the cytoplasm and the transcellular secretion of water into the salivary ducts.[4, 6, 7] **Figure 1: Normal neurotransmitter release**  **Source:** Adapted from Arnon SS *et al.* (2001).[8] Xeomin is an acetylcholine release inhibitor which inhibits presynaptic acetylcholine release from the parasympathetic nerve terminals supplying the salivary glands. By infiltrating cholinergic nerve terminals and degrading the synaptosome associated protein (SNAP)-25 proteins, Xeomin blocks the fusion of neurosecretory vesicles with the plasma membrane, and hence the release of acetylcholine, as shown in Figure 1.[9] This inhibition of cholinergic transmission at the neuroglandular junction results in a reduction in saliva production. In turn, this reduction in the amount of saliva present in the mouth leads to a reduced rate of anterior and posterior loss of saliva.

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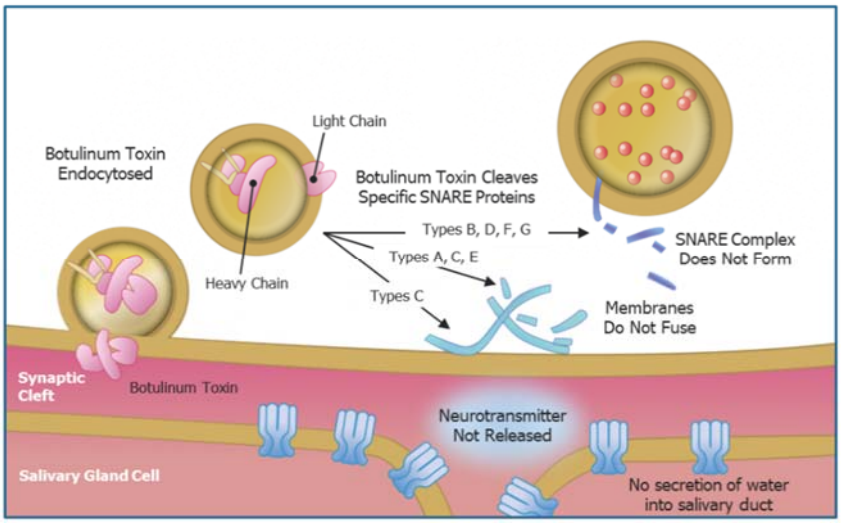
<table>
<tr><td></td><td>Figure 2: Mechanism of action of Xeomin
 

Source: Adapted from Arnon SS et al. (2001).[8]</td></tr>
<tr><td>Marketing authorisation/CE mark status</td><td>A marketing authorisation application for Xeomin for the treatment of chronic sialorrhoea was submitted to the European Medicines Agency (EMA) on [redacted] and a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) is expected on [redacted].</td></tr>
<tr><td>Indications and any restriction(s) as described in the summary of product characteristics (SmPC)</td><td>The anticipated EU marketing authorisation wording for Xeomin in the indication of interest for this submission is: “Xeomin for the treatment of chronic sialorrhoea.”
Contraindications
Hypersensitivity to the active substance botulinum neurotoxin type A or the following excipients: human albumin; sucrose
Generalised disorders of muscle activity (e.g. myasthenia gravis, Lambert-Eaton syndrome)
Infection or inflammation at the proposed injection site.</td></tr>
<tr><td>Method of administration and dosage</td><td>Administration
Xeomin is injected into the parotid and submandibular glands on both sides (i.e., 4 injection sites per treatment session)
Xeomin may only be administered by physicians with suitable qualifications and the requisite experience in the application of Botulinum toxin type A
The salivary glands can be located using ultrasound imaging or surface anatomical landmarks
Dosage
The recommended total dose per treatment session is 100 units (U), no sooner than every 16 weeks.
The dose is divided with a ratio of 3:2 between the parotid and submandibular glands (see below)
<table>
<tr><th>Gland</th><th>Units per side</th><th>Total</th></tr>
<tr><td>Parotid gland(s)</td><td>30 U</td><td>60 U</td></tr>
<tr><td>Submandibular gland(s)</td><td>20 U</td><td>40 U</td></tr>
<tr><td>Both glands</td><td>50 U</td><td>100 U</td></tr>
</table></td></tr>
<tr><td>Additional tests or investigations</td><td>No specific additional tests or investigations are associated with the administration of Xeomin.</td></tr>
</table>

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List price and average cost of a course of treatment	• List price: Xeomin 100 unit powder for solution for injection vial: £129.90[10] • The annual cost of treatment with Xeomin is £422.18 (£129.90 x 3.25 16-week cycles).
Patient access scheme (if applicable)	N/A: No patient access scheme is available or being considered for Xeomin in this indication.

Abbreviations: CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; EU: European Union; N/A: not applicable; SNAP: synaptosome associated protein; U: units.

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

B.1.3.1 Disease overview

The term sialorrhoea describes the unintentional loss of saliva from the mouth. This includes both anterior loss (visible loss of saliva beyond the lip margin) and posterior loss (the spillage of saliva from the oral cavity into the pharynx) of saliva.[11] However, sialorrhoea is an inconsistently defined term and is also sometimes used to refer to the production of excess saliva (hypersalivation). This submission focusses on sialorrhoea (rather than hypersalivation) i.e. the unintentional anterior and posterior loss of saliva from the mouth.[12]

Whilst sialorrhoea is common in infants, it is abnormal after the age of four, though it may persist in children with neurological conditions such as cerebral palsy.[13] In adults, sialorrhoea can develop as a symptom of neurological conditions such as motor neurone disease or Parkinson's disease, or as a result of strokes or head and neck injuries. It can be also be a side effect of taking some types of drugs, including benzodiazepines, neuroleptics and cholinesterase inhibitors. The anticipated EMA licence for Xeomin is broad; in line with the FDA licence received in July 2018, Xeomin is anticipated to be licensed for the treatment of adults with chronic sialorrhoea, regardless of aetiology.[2]

The pathophysiology of sialorrhoea is unclear, and the anterior or posterior loss of saliva can result from a combination of related functional problems. Saliva is continuously produced from a variety of salivary glands, chiefly the parotid, submandibular and sublingual glands, and hypersecretion of saliva from these glands can be a contributing factor to sialorrhoea.[14] Anatomical abnormalities and poor oral and facial muscle control can also result in loss of salivary continence with or without excessive saliva production.[15] For patients with neurological disorders such as cerebral palsy or Parkinson's disease, weakened facial musculature leading to ineffective swallowing, inadequate rate of swallowing and poor lip seal are thought to be the primary causes of sialorrhoea, rather than increased saliva production.[16]

Disease burden

Sialorrhoea is associated with a variety of negative sequelae including perioral dermatitis, poor oral hygiene, bad breath, increased amount of intra-oral occult bacteria, eating and speaking difficulty, sleep disturbance, dehydration and fatigue.[12, 15, 17] In many patients with neurological conditions these symptoms will be accentuated by muscle weakness or dystonia in the neck, trunk or limbs, causing a flexed posture and/or difficulty maintaining oral hygiene, contributing further to the debilitating nature of the condition. Anterior loss of saliva may also cause saliva to pool at the back of the throat which, in addition to contributing to the sensation of choking and anxiety, can lead to the development of life-threatening aspiration pneumonia if saliva is

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inhaled.[15, 18] Feedback from UK clinical experts experienced in the treatment of sialorrhoea indicated that 5–10% if patients with sialorrhoea may experience an occurrence of aspiration pneumonia, which can which can entail traumatic hospital episodes for patients and incur substantial costs to the health system.[1, 19]

Furthermore, sialorrhoea can have a considerable psychosocial impact on patients through social embarrassment and decreased self-esteem, which can lead to social isolation.[12, 18] Barriers to education through damage to books or electronic devices present further difficulties to patients with sialorrhoea.[12] As a result, sialorrhoea can have a considerable detrimental effect on the quality of life (QoL) of both patients and carers. Finally, sialorrhoea can increase the burden on caregivers who may already be supporting the patient in managing the severe consequences of neurological disease; this can lead to depression and anxiety, and consequent reductions in caregiver QoL which are not captured within the cost-effectiveness analysis for this submission.[17]

Epidemiology

Xeomin is anticipated to be licensed for the treatment of adults with chronic sialorrhoea, regardless of aetiology. Patients may develop sialorrhoea due Parkinson's disease, motor neurone disease, stroke or cerebral palsy, in addition to traumatic or acquired brain injury, or as the side effect of taking some types of drugs, including benzodiazepines, neuroleptics and cholinesterase inhibitors. Reliable population estimates of the incidence of these conditions and the proportion of patients who may be suffering from sialorrhoea are limited.[20] The prevalence of sialorrhoea in Parkinson's disease could be as high as 84%, and is estimated to range between 10-80% in patients with cerebral palsy.[21]

Given the difficulty in accurately estimating the total Xeomin-eligible patient population from the literature, feedback from a survey of UK clinical experts conducted by Merz was utilised.[22] Based on this survey, the proportion of patients with Parkinson's disease who have sialorrhoea was estimated to be 22.50%, of which 63.48% were considered to require treatment for sialorrhoea. Data from the clinician survey also estimated that, of the total patients managed in clinical practice for sialorrhoea, 37.62% would have Parkinson's disease.[1]

As such, given the availability of data on the incidence and prevalence of Parkinson's disease in England, the total number of prevalent Parkinson's disease patients (124,031) anticipated to be suffering from sialorrhoea is estimated to be 27,907, of which 17,715 patients would have a treatment need for sialorrhoea.[22, 23] Using this value as a fixed proportion (37.62%) of the total number of patients with sialorrhoea in England and by scaling up, the total number of prevalent patients with a treatment need for sialorrhoea in England is estimated to be 47,090. Similarly, the annual incident number of patients with Parkinson's disease in England is estimated to be 17,829 (based on an incident rate of 0.04%), of which 4,011 are anticipated to be suffering from sialorrhoea, and 2,546 have a treatment need for sialorrhoea.[22, 23] scaling up, the total number of incident patients with a treatment need for sialorrhoea in England per year is estimated to be 6,769.

In summary, sialorrhoea is expected to affect a very large population in England, who have an extremely high unmet need for an effective therapy. Further details of the patient population estimates are presented in the budget impact analysis template.

B.1.3.2 Clinical pathway of care

There are no national guidelines focused on sialorrhoea in its own right, but a Q&A document intended as a guide for NHS healthcare professionals is available from the Southampton

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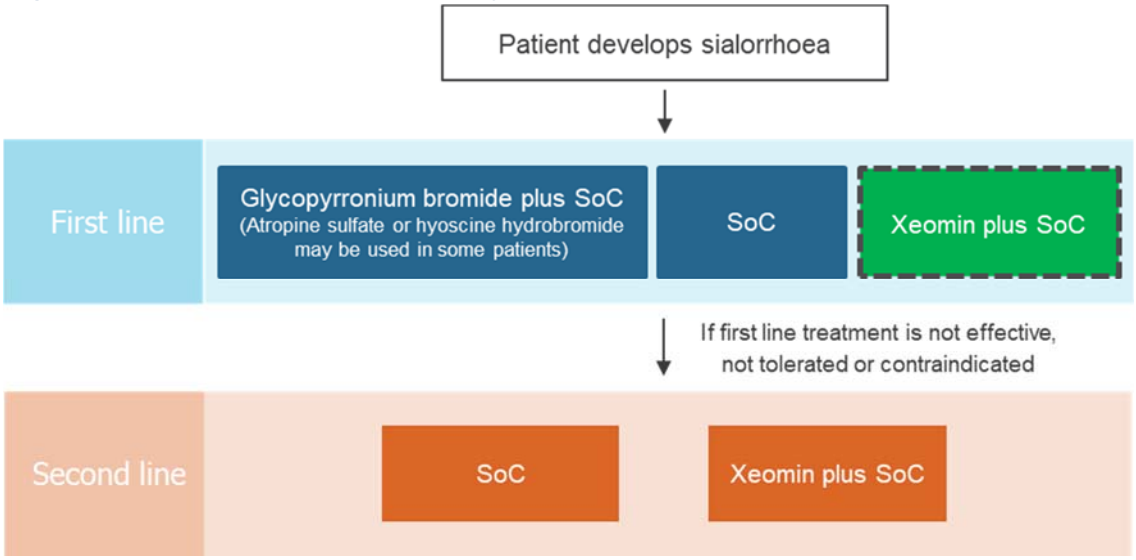
Medicines Advice Service (UKMi) for the treatment of hypersalivation.[16] Within these guidelines, patient-specific management is recommended due to the multifactorial nature of the condition, which may require a multidisciplinary team approach using a combination of treatments. These may include practical aids, speech therapy, behaviour therapy, physiotherapy, radiotherapy, surgery and active therapy.[16]

Considerations for the treatment of sialorrhoea as a consequence of particular neurological conditions have been included in several clinical guidelines published by NICE, including Parkinson's disease in adults (NG71, July 2017), cerebral palsy in under 25s (NG62, August 2016) and motor neurone disease (NG42, September 2015).[24-26] Both NG62 and NG42 state that anticholinergic therapies, such as glycopyrrolate (glycopyrronium bromide) and transdermal hyoscine hydrobromide, can be considered for the first-line pharmacological management of sialorrhoea,[24-26] though the Parkinson's disease (NG71) guidelines recommend that pharmacological management of drooling should only be considered if non-pharmacological management (e.g. speech and language therapy) is not available or has not been effective.[8]

Despite recommendations by NICE to consider the use of anticholinergic therapies for the first-line pharmacological management of sialorrhoea, there are currently no anticholinergic therapies licensed for use in sialorrhoea in adults in the UK, thus all use of anticholinergic therapies in this indication is off-label. This highlights the lack of clinical evidence supporting the use of anticholinergic therapies as effective treatment options in this indication, and the unmet need for a highly effective, licensed treatment option for patients in this setting. As summarised in the UKMi Q&A document, there are no well-designed, large randomised studies that compare the different therapeutic options available for the management of sialorrhoea.[27]

Feedback from UK clinical experts experienced in the clinical management of sialorrhoea indicated that sialorrhoea is heavily untreated; the majority of patients do not receive active therapy, and their sialorrhoea is instead managed with basic non-pharmacological management (SoC), which may include practical aids, such as bibs, as well as speech, language and occupational therapy. For patients who do who do receive active therapy, one of the most commonly prescribed therapies is oral glycopyrronium bromide, which is considered the most relevant active comparator to Xeomin in the context of this submission (Figure 3). Some patients also receive treatment with transdermal hyoscine hydrobromide, or sublingual atropine sulfate.[1]

Figure 3: Anticipated clinical pathway of care for adult patients with chronic sialorrhoea



Abbreviations: SoC: standard of care.

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Whilst oral glycopyrronium bromide is licensed for use in children and adolescents (aged three years and older) with neurological disorders, long-term efficacy and safety data are lacking, and it is unlicensed in adults.[28] Additionally, as cholinergic transmission is vital to the correct functioning of organs such as the bladder and both glycopyrronium bromide and hyoscine hydrobromide work by reducing the cholinergic stimulation of salivary glands, anticholinergic therapies are therefore associated with numerous unwanted effects in other organ systems, including urinary retention, constipation, increased intraocular pressure, cessation of perspiration with increased body temperature and double vision.[15, 29, 30] Treatment with topical hyoscine hydrobromide patches often has to be stopped due to the severity of associated skin irritation, and anticholinergic treatment can also interfere with the central nervous system, resulting in intolerable adverse effects such as memory problems, confusion, sedation, nausea, and disorientation.[15, 29, 31, 32] Excessively dry mouth has also been associated with anticholinergic treatment, and can cause further deterioration of patient QoL.[15, 29, 32]

Finally, the NICE evidence summary for oral glycopyrronium bromide for the treatment of hypersalivation (ESUOM15) reflects the above limitations, concluding the following:[33]

- There is only *"moderate evidence that oral glycopyrronium bromide (tablets and solution or suspension) reduces hypersalivation (sialorrhoea) or drooling in children and young people with a neurological condition, and adults with Parkinson's disease, compared with placebo"*
- There is *"limited evidence of its efficacy in adults with schizophrenia and clozapine-induced hypersalivation"*
- There is *"no evidence of its long-term efficacy or safety in treating hypersalivation"*
- *"Oral glycopyrronium bromide has been associated with more adverse effects and discontinuations because of adverse effects than placebo"*

Positioning of Xeomin

Botulinum toxin type A is currently recommended in the NICE clinical guidelines mentioned above if treatment with anticholinergic therapies is not effective, not tolerated or contraindicated. It is important to note that evidence from the SIAXI trial, the pivotal phase III randomised controlled trial (RCT) for patients receiving Xeomin in the first-line setting, has not been considered within these guidelines:

- ***NG71:*** *"Consider glycopyrronium bromide to manage drooling of saliva in people with Parkinson's disease. If treatment with glycopyrronium bromide is not effective, not tolerated or contraindicated (for example, in people with cognitive impairment, hallucinations or delusions, or a history of adverse effects following anticholinergic treatment), consider botulinum toxin A"*[24]
- ***NG42:*** *"Consider a trial of anticholinergic medicine as the first-line treatment for sialorrhoea in people with MND. Consider glycopyrrolate as the first-line treatment for patients who have cognitive impairment, because it has fewer central nervous system side effects. If first-line treatment is not effective, not tolerated or contraindicated, consider botulinum toxin A"*[26]
- ***NG62:*** *"To reduce the severity and frequency of drooling in children and young people with cerebral palsy, consider transdermal hyoscine hydrobromide. If transdermal hyoscine hydrobromide is contraindicated, not tolerated or not effective, consider glycopyrrolate. Consider specialist assessment and use of botulinum toxin A injections to the salivary glands*

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with ultrasound guidance to reduce the severity and frequency of drooling if anticholinergic drugs provide insufficient benefit or are not tolerated"[25]

In this submission, Xeomin is positioned for the first-line treatment for patients with sialorrhoea, in line with the clinical evidence base provided by the pivotal SIAXI clinical trial for Xeomin reported in Section B.2 and the comparators specified in the NICE final scope for this appraisal. Based on feedback from UK clinical experts, if patients in this setting are treated with active therapy, then one of the most commonly tried anticholinergic therapies is oral glycopyrronium bromide. For patients who do not currently receive active therapy, or for patients in whom anticholinergic therapies are unsuitable, non-pharmacological management represents the SoC.[1] Therefore, oral glycopyrronium bromide and SoC are considered to represent the most relevant comparators to Xeomin in the context of this appraisal.

B.1.4 Equality considerations

No equality issues related to the use of Xeomin in this indication have been identified or are foreseen.

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B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A clinical SLR was conducted in August 2018 to identify relevant clinical evidence of the efficacy and safety of Xeomin for the treatment of chronic sialorrhoea. The SLR was performed in accordance with the methodological principles of conduct for systematic reviews as detailed in the University of York Centre for Reviews and Dissemination's "Guidance for Undertaking Reviews in Health Care".[34] Given the availability of RCT data in this indication, it was considered appropriate to search for RCT data only within the SLR.

The searches for the SLR identified a total of 2,542 unique records, of which 2,482 records were excluded following abstract review. A further 36 records were excluded following full-text review, hence a total of 25 publications reporting on 17 unique RCTs were ultimately included within the SLR.

Of these, two RCTs were identified that reported clinical evidence on the efficacy and safety of Xeomin for the treatment of chronic sialorrhoea: SIAXI (NCT02091739) and a small cross-over study (NCT01653132). Five publications were identified for the SIAXI trial (all conference abstracts) and one publication was identified for the crossover study.[35-39]

Full details of the SLR search strategy, study selection process and results can be found in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

As described above, two RCTs were identified from the SLR that provide evidence for the clinical efficacy and safety of Xeomin in patients with chronic sialorrhoea: SIAXI (NCT02091739) and a small cross-over study (NCT01653132). An overview of these trials is presented in Table 3.

The SIAXI trial represents the pivotal clinical trial for Xeomin in this indication; therefore, due to its small sample size (N=10), the crossover study (NCT01653132) presented in Table 3 below is not considered further within this submission.

Table 3: Clinical effectiveness evidence

Study	SIAXI (NCT02091739).	NCT01653132.
Study design	Phase III, prospective, randomised, double-blind, placebo-controlled, parallel-group, multicentre study.	US-based, single centre, randomised, double-blind, placebo-controlled crossover trial.
Population	Patients with chronic troublesome sialorrhoea due to Parkinson's disease or atypical parkinsonism (multiple system atrophy, corticobasal degeneration, or progressive supranuclear palsy) or after stroke or traumatic brain injury.	Patients with troublesome drooling due to Parkinson's disease.
Intervention(s)	Xeomin (incobotulinumtoxin toxin A) Administered as four injections (total: 75 U or 100 U) into bilateral parotid and bilateral submandibular salivary glands per treatment cycle (16 weeks): 22.5 U and 15 U respectively per side in the 75 U group, and 30 U and 20 U respectively per side in the 100 U group.	Xeomin (incobotulinumtoxin toxin A) Administered as four injections (total dose 100 U) into bilateral parotid and bilateral submandibular salivary glands: 20 U and 30 U respectively per side in the 100 U group.

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Comparator(s)	Volume-matched placebo vials containing excipients of Xeomin.	1ml placebo (sterile, preservative free 0.9% saline).
Trial supports application for marketing authorisation	Yes.	No.
Trial used in the economic model	Yes.	No.
Rationale for use/non-use in the model	SIAXI is the pivotal clinical study informing the marketing authorisation of Xeomin in this indication.	Small sample size (n=10), and other more robust evidence is available from the SIAXI trial.
Reported outcomes specified in the decision problem	• Unstimulated salivary flow rate (uSFR) • Global Impression of Change Scale (GICS) • Adverse effects of treatment (TEAE, TEAESI, TESAE) • Health-related quality of life: EQ-5D-3L (VAS and single items)	• Adverse effects of treatment (AEs)
All other reported outcomes	• Drooling Severity and Frequency Scale (DSFS) • Modified Radboud Oral Motor Inventory for Parkinson's disease (mROMP) swallowing symptoms score • Length of between-treatment interval • Vital signs (blood pressure, heart rate) • Clinical chemistry (alkaline phosphatase, blood glucose) • Dental and oral examination	• Difference in saliva weight • Drooling Severity and Frequency Scale (DSFS) • Unified Parkinson's Disease Rating Scale (UPDRS) parts two and three

Abbreviations: DSFS: Drooling Severity and Frequency Scale; EQ-5D-3L: EuroQoL 5-dimensions 3-levels; GICS: Global Impression of Change Scale; TEAE: treatment-emergent adverse events; TEAESI: treatment-emergent adverse events of special interest; TESAE: treatment-emergent serious adverse events; U: units; US: United States; uSFR: unstimulated salivary flow rate; VAS: visual analogue scale.
Source: SIAXI Interim Clinical Study Report (16th May 2017),[40] Blitzer *et al*. (2017),[35] Narayanaswami *et al*. (2016).[41]

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

B.2.3.1 Trial design and methodology

The SIAXI trial is a completed Phase III, prospective, randomised, double-blind, placebo-controlled, parallel-group, multicentre study comprising four consecutive treatment cycles with one of two dose levels of Xeomin or placebo in adults with chronic troublesome sialorrhoea due to a variety of neurological conditions.[35]

A summary of the methodology of the SIAXI trial is presented in Table 4, and the full inclusion and exclusion criteria of the SIAXI trial are presented in Appendix D.

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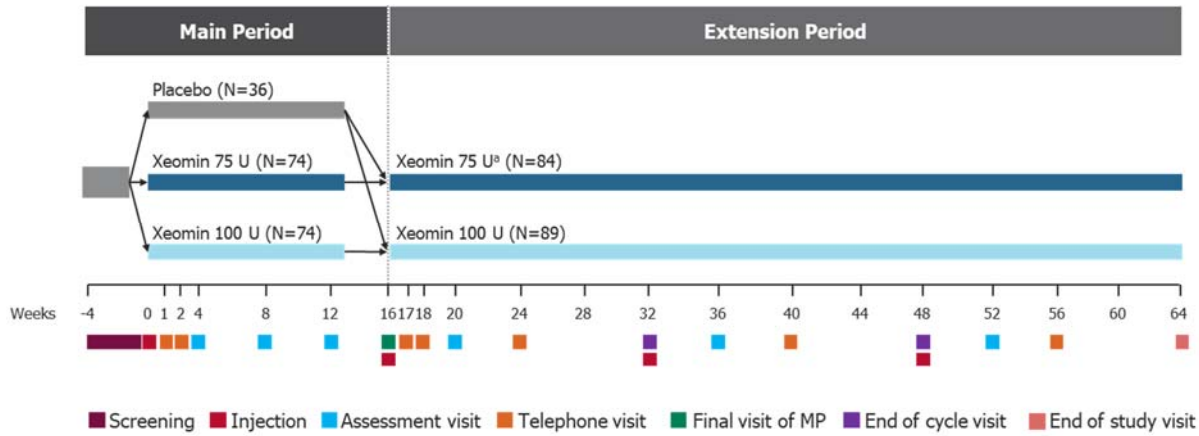
The trial included two treatment periods: the main period (MP) and an extension period (EP). Patients in the MP were randomised in a ratio of 2:2:1 into three treatment groups: two groups received active Xeomin treatment (75 U or 100 U, in a ratio of 1:1, respectively) and one group received placebo. The MP comprised one treatment cycle (16±2 weeks). Xeomin or placebo was administered at the beginning of the cycle as four bilateral injections into the parotid and submandibular glands: 22.5 U and 15 U, respectively, per side in the 75 U group, and 30 U and 20 U, respectively, per side in the 100 U group. Patients either returned to the study site or were contacted by telephone for assessment visits over the total MP duration of 16±2 weeks, as shown in Figure 4. At the end of the placebo-controlled MP, patients were examined for eligibility to enter the EP.[35]

Eligibility for the EP was based on a clinical need for continued treatment and a lack of medically relevant moderate or severe adverse events of special interest, among other criteria. Full details of the eligibility criteria for the EP are presented in Appendix D. All patients who entered the EP received Xeomin but were blinded with respect to dose level (100 U or 75 U). Patients who had been randomised to one of the groups receiving Xeomin in the MP stayed in their respective dose group (100 U of 75 U), while patients who were treated with placebo in the MP were randomised (in a ratio of 1:1) to receive either 100 U or 75 U of Xeomin in the EP. The EP comprised three treatment cycles (each 16±2 weeks) and concluded with an end-of-study examination at the end of the final cycle.[35]

The overall study design of the SIAXI trial, including injection visits, telephone contact and assessment visits, is summarised in Figure 4. Including the screening period of at most 4 weeks as an initial part of the MP, the total study duration was 64 weeks (range 56–72 weeks). Overall, 184 patients were randomised and treated in the MP: 74 patients in each of the Xeomin dose groups and 36 patients in the placebo group.[35] A total of 173 patients completed the MP and entered the EP: 89 patients were treated with 100 U of Xeomin and 84 patients were treated with 75 U of Xeomin.

Figure 4: Summary of SIAXI trial design



[a] If dose reduction (still blinded) for subjects receiving 75 U in the MP became necessary in the EP, then for the study analysis a 3rd dose group was introduced (56 U, corresponding to 25% reduction of 75 U). Dose reduction was allowed only once and in only one step. Furthermore, it was allowed only at the 3rd/4th injection as an alternative to withdrawal of the subject due to AEs.
Abbreviations: U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017),[40] Blitzer *et al*. (2017).[35]

The co-primary objectives of the SIAXI trial were to evaluate the efficacy of Xeomin in terms of the change from baseline to Week 4 in unstimulated salivary flow rate (uSFR) and the patient's

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Global Impression of Change Scale (GICS) entry at Week 4 (or carer's GICS entry, if the patient was not able to answer).[35] A summary of the SIAXI trial methodology is presented in Table 4.

Table 4: Summary of the SIAXI trial methodology

Trial name	SIAXI (NCT02091739)
Location	International: 33 sites (12 sites in Germany, 21 in Poland)
Trial design	Phase III, prospective, randomised, double-blind, placebo-controlled, parallel-group, multicentre study • Main Period (MP): 16±2 weeks • Extension Period (EP): 48±6 weeks
Eligibility criteria for participants	A summary of the inclusion and exclusion criteria are provided below. Full details of eligibility criteria of the SIAXI trial are presented in Appendix D. **Key inclusion criteria** • Documented diagnosis of the basic neurological condition associated with sialorrhoea (Parkinson's disease or atypical parkinsonism, stroke, or traumatic brain injury); with its onset at least 6 months before screening) • Chronic troublesome sialorrhoea related to parkinsonism or stroke or traumatic brain injury (for at least 3 months) at screening, defined as the presence of all of the following, at screening and at baseline and for at least the 3 months, before screening (where retrospective response to questionnaires was impossible, a statement of equivalent severity sufficed): o A Drooling Severity and Frequency Scale [DSFS] sum score of at least 6 points and o A score of at least 2 points for each item of the DSFS and o A score of at least 3 points on the modified Radboud Oral Motor Inventory for Parkinson's disease [mROMP], Section III 'Drooling', Item A) • A score of at most 2 points on the mROMP Section II 'swallowing symptoms' Item A) and a score of at most 3 points on Item C), at screening and at baseline **Key exclusion criteria** • Non-neurological secondary causes of sialorrhoea. • Unstable concomitant medication influencing sialorrhoea (such as anticholinergics for the treatment of parkinsonism); dosages of these medications had to be stable for at least 4 weeks before study entry, i.e., screening, and had to be planned to remain stable during the course of the study • Recent (i.e., 4 weeks) drug treatment for sialorrhoea • History of recurrent aspiration pneumonia • Extremely poor dental/oral condition as assessed by a qualified dentist • Recent (i.e., 1 year for sialorrhoea, 14 weeks for other indications) treatment with – or known hypersensitivity to – Botulinum toxin [BoNT] or known hypersensitivity to any ingredient of the study preparation • Recent (i.e., 4 weeks) changes in anti-parkinsonian medication • Previous or planned surgery or irradiation to control sialorrhoea
Method of study drug administration	Administered as four injections (75 U or 100 U) into bilateral parotid and bilateral submandibular salivary glands per treatment cycle (16±2 weeks) • 75 U: 22.5 U (0.6 mL) and 15 U (0.4 mL) in the parotid and submandibular glands, respectively, per side • 100 U: 30 U (0.6 mL) and 20 U (0.4 mL) in the parotid and submandibular glands, respectively, per side

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	• Equivalent volumes were injected into each gland in the placebo group
Permitted and disallowed concomitant medication	The following medications were forbidden or restricted during the study: • Botulinum neurotoxin (other than the study treatment) during the screening period and/or planned for any time during the entire study period • Aminoglycoside antibiotics, curare-like agents, or other agents that might interfere with neuromuscular function • Pharmacological treatment for sialorrhoea or concomitant medication influencing sialorrhoea (e.g. anticholinergics) during the 4 weeks before baseline or planned for the time of the MP • In indications such as parkinsonism, drugs with an anticholinergic mode of action were only allowed if they were taken at a stable dosage for the entire time from (at least) 4 weeks before screening to the end of the MP • Medication known to cause hypersalivation (e.g. clozapine) • Anticoagulants (e.g. warfarin) (Note: platelet-aggregation inhibitors and acetylsalicylic acid were allowed) • Change in dose regimen of medications(s) to treat Parkinson's disease or atypical parkinsonism within the 4 weeks before screening or planned for the time of the MP The following non-drug therapies were forbidden: • Salivary gland surgery or irradiation during the entire study period (including the screening period) • Planned surgery in any indication during the screening period or (with the exception of minor surgery outside the head and neck region) planned for any time during the MP
Primary outcomes	**Co-primary outcomes:** • uSFR: change from baseline to Week 4 • GICS entry (or carer's GICS entry, if the patient was not able to answer) at Week 4
Secondary and other outcomes	A summary of the secondary outcomes is provided below: • uSFR: change from baseline to Week 8 and 12 • Patient's GICS entry (or carer's GICS entry, if the patient was not able to answer) at Weeks 1, 2, 8, and 12 • DSFS • mROMP • EQ-5D-3L • AEs, TEAEs, TEAESIs and TESAEs
Pre-planned subgroups	In the MP, subgroup analyses were performed for uSFR, patient's GICS, DSFS by aetiology of sialorrhoea, method of administration, gender, and country In the EP, subgroup analyses were performed for uSFR, patient's GICS and DSFS by method of administration for the EP
Duration of study and follow-up	The total study duration was 64 weeks (range 56–72 weeks), which includes a screening period of at most 4 weeks as an initial part of the MP

Abbreviations: BoNT: botulinum toxin; DSFS: Drooling Severity and Frequency Scale; EP: extension period; GICS: Global Impression of Change Scale; MP: main period; mROMP: modified Radboud Oral Motor Inventory for Parkinson's disease; TEAEs: treatment emergent adverse events; TEAESIs: treatment emergent adverse events of special interest; TESAE: treatment emergent serious adverse events; uSFR: unstimulated salivary flow rate.
Source: SIAXI Interim Clinical Study Report (16th May 2017),[40] Blitzer *et al*. (2017).[35]

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B.2.3.2 Baseline characteristics

An overview of the baseline characteristics of patients included in the MP of the SIAXI trial is presented in Table 5.[40] Overall, patient baseline characteristics were comparable between the three groups in the MP. Patients were between the ages of 21 and 80 years old (mean 65.2 years) and the majority of patients were male (70.7%) and white (99.5%). The majority of patients suffered from Parkinson's disease (70.7%), and the aetiology of sialorrhoea was similar between the treatment groups. The baseline characteristics of patients who entered the EP were consistent with those who entered the MP.[40] Full details of the baseline characteristics and proportion of patients receiving ultrasound guidance in the EP can be found in Appendix L.

Feedback from UK clinical experts experienced in the treatment of sialorrhoea indicated that the baseline characteristics of the patients within the SIAXI trial were comparable to those patients seen with sialorrhoea in UK clinical practice.[1] Furthermore, the anticipated licence for Xeomin is broad, and does not specify the aetiology of sialorrhoea. The mechanism of action of Xeomin is also such that treatment effect is independent of the aetiology of the sialorrhoea. Therefore, and as recognised by the EMA in their provision of a broader licence for Xeomin, there is no reason to suggest that the efficacy of Xeomin observed within the SIAXI trial would not translate to patients suffering from sialorrhoea due to conditions outside of those suffered by the patients within the SIAXI trial.

Table 5: Baseline characteristics of patients included in the Main Period of the SIAXI trial

Characteristics	Xeomin 100 U (N=74)	Xeomin 75 U (N=74)	Placebo (N=36)	Total (N=184)
Sex (n [%])				
Male	52 (70.3)	50 (67.6)	28 (77.8)	130 (70.7)
Female	22 (29.7)	24 (32.4)	8 (22.2)	54 (29.3)
Age (years)				
n	74	74	36	184
Mean (SD)	66.0 (11.6)	65.2 (11.7)	63.5 (10.6)	65.2 (11.4)
Median	67.5	67.0	64.0	66.5
Min, max	21, 80	27, 80	23, 80	21, 80
Age group (n [%])				
18-64 years	28 (37.8)	30 (40.5)	19 (52.8)	77 (41.8)
65-84 years	46 (62.2)	44 (59.5)	17 (47.2)	107 (58.2)
≥85 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Race (n [%])				
White	73 (98.6)	74 (100.0)	36 (100.0)	183 (99.5)
Asian	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.5)
Ethnicity (n [%])				
Hispanic or Latino	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.5)
Not Hispanic or Latino	73 (98.6)	74 (100.0)	36 (100.0)	183 (99.5)
Weight (kg)				
n	74	74	36	184
Mean (SD)	79.8 (14.0)	78.4 (17.1)	80.6 (16.4)	79.4 (15.7)
Median	79.0	78.0	81.4	79.0

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Min, max	49, 116	37, 127	50, 128	37, 128
BMI (kg/m2)				
n	74	74	36	184
Mean (SD)	27.7 (3.8)	26.7 (5.2)	28.5 (6.0)	27.5 (4.9)
Median	27.5	26.4	28.3	27.5
Min, max	19, 35	14, 51	19, 41	14, 51
Drooling aetiology, n (%)				
Parkinson's disease	53 (71.6)	51 (68.9)	26 (72.2)	130 (70.7)
Atypical parkinsonism	5 (6.8)	8 (10.8)	3 (8.3)	16 (8.7)
Stroke	14 (18.9)	13 (17.6)	6 (16.7)	33 (17.9)
Traumatic brain injury	2 (2.7)	2 (2.7)	1 (2.8)	5 (2.7)
uSFR; mean (SD)	0.40 (0.27)	0.42 (0.28)	0.38 (0.23)	0.40 (0.26)
DSFS; mean (SD)	6.78 (0.90)	6.88 (0.91)	6.97 (1.06)	6.86 (0.93)
Injection guidance, n (%)				
Ultrasound guided	41 (55.4)	45 (60.8)	18 (50)	104 (56.5)
Anatomical landmarks guided	33 (44.6)	29 (39.2)	18 (50)	80 (43.5)

Abbreviations: BMI: body mass index; DSFS, drooling severity and frequency scale; max: maximum; min: minimum; PD: Parkinson's disease; SD: standard deviation; uSFR, unstimulated salivary flow rate.
Source: SIAXI Interim Clinical Study Report (16th May 2017),[40] Blitzer *et al*. (2017).[35]

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

Trial populations

The definitions of the analysis sets used in the analysis of the SIAXI trial are presented in Table 6 below.[40]

Table 6: Trial populations used for the analysis of outcomes of the SIAXI trial

Analysis set	Description
Main Period	
Full Analysis Set (FAS; n=184)	• Comprises all patients who were treated and had at least the baseline value of uSFR • Analyses of co-primary and secondary efficacy variables were performed on the FAS
Per Protocol Set (PPS; n=165)	• Comprises patients in the FAS without major protocol deviations • Sensitivity analyses were performed using the PPS for the co-primary and all secondary efficacy variables
Safety Evaluation Set (SES; n=184)	• Comprises all patients who received study medication (Xeomin or placebo) during the MP of the study
Extension Period	
Safety Evaluation Set (SES-EP; n=173)	• Comprises all patients who received study medication (Xeomin) at least once during the EP of the study

Abbreviations: EP: extension period; FAS: full analysis set, MP: main period; PPS: per protocol set; SES: safety evaluation set, SES-EP: safety evaluation set of the extension period; uSFR: unstimulated salivary flow rate.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

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Analysis of co-primary endpoints

The co-primary endpoints of the SIAXI trial were change from baseline in uSFR and the patient's GICS entry (or carer's GICS entry, if the patient was not able to answer) at Week 4.[35] Statistical analysis for the co-primary endpoints was performed on the FAS using the MMRM approach with comparisons of LS-Means using a fixed sequence test procedure. Statistical significance was defined as $p<0.05$. Full details of the statistical methods used for the primary analyses in SIAXI are presented in Table 7.[40]

Analysis of secondary endpoints

All secondary endpoints were analysed analogously to the co-primary efficacy variables. All tests were descriptive and interpreted in an explorative manner.

Analysis of safety endpoints

All safety endpoints were analysed for the SES using descriptive summary statistics.

Interim analyses

A database snapshot was taken on 1st February 2016 after all patients had completed (or discontinued from) the MP. MP treatment was then unblinded and analyses were performed on the co-primary and secondary efficacy variables. In addition, an interim snapshot of the long-term efficacy and safety data from the trial was generated on the 7th November 2016 for regulatory purposes. This was based on patients in the EP who had been receiving 75 U or 100 U Xeomin during the MP and were hence unblinded during the EP. At this time, the allocation of patients who had received placebo during the MP to 75 U or 100 U in the EP was still blinded.

The database for the trial was closed after completion of the EP on the 4th January 2017 and an overall study report was prepared for the entire study. None of the data used for analysing the MP efficacy (including the confirmatory primary analysis) had been changed from the database snapshot on the 1st February 2016 to database closure on the 4th January 2017, therefore all MP data analyses were based on blinded patients/investigators.

Table 7: Statistical methods for the primary analysis of SIAXI

Trial name	SIAXI
Hypothesis objective	The primary efficacy analysis was performed by testing the null hypotheses that there was no difference between Xeomin (100 U and 75 U) and placebo groups in change in uSFR and GICS from baseline to Week 4, against the alternative hypothesis that there was a difference between these groups, at overall two-sided 5% level of significance. Overall superiority of Xeomin over placebo in both dose groups was only verified if the null hypotheses (uSFR and GICS) were rejected for the 100 U group, as per a fixed sequence test procedure which first compared the Xeomin 100 U treatment group with placebo, followed by comparison of the 75 U group with placebo if the results of the first tests were significant.
Statistical analysis	• A mixed model repeated measurement analysis (MMRM) (2-sided, significance level α=0.05) with comparison of least square means (LS-Means) was used for the confirmatory analysis of the primary (change in uSFR) and the co-primary (GICS) efficacy variable regarding differences between the treatment groups • The dependent variable was the change from baseline in uSFR or GICS, respectively. The independent variables were defined as treatment group, aetiology subset, use of ultrasound, country and gender as fixed factor, visit*treatment as interaction term, and visit as repeated factor • To adjust for the baseline status, the MMRM of the primary efficacy variable

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	additionally included the baseline score of the uSFR as a covariate. Since no baseline assessment of the co-primary efficacy variable (GICS at Week 4) was available, the baseline DSFS was used as covariate in the MMRM model of the co-primary efficacy variable instead • Secondary efficacy analyses (change from baseline to Weeks 8 and 12 in uSFR, and patient's GICS entry at Weeks 1, 2, 8 and 12) were carried out in an analogous manner to the primary efficacy analyses • Statistical analyses of other efficacy variables are summarised in the CSR. • The confirmatory analyses of the co-primary outcomes were performed on the FAS, and sensitivity analyses were performed using the same approach on the PPS • Sensitivity analyses were also performed to investigate the impact of missing values and different approaches for imputation (see below) • Furthermore, a non-parametric Wilcoxon rank-sum test was performed as a sensitivity analysis of the co-primary efficacy variables to investigate the impact of potential deviations from the assumption of normal distribution (FAS and PPS, using BOCF and OC analysis for uSFR) • Results obtained in these analyses confirmed the results of the initial analyses, so they have not been presented in this submission.
Sample size, power calculation	• A total of 180 treatment-naïve patients were planned to be randomised to Xeomin with a ratio of 2:2:1 – i.e., in the MP, 72 patients to receive 75 U of Xeomin, 72 patients to receive 100 U of Xeomin, and 36 patients to receive placebo • The sample size was calculated separately for safety and for each primary efficacy variable (uSFR and GICS) as follows: o Safety: On the basis of a 2:2:1 randomisation ratio and an assumed drop-out rate of 30% over a year, and a minimum of 50 treated patients in the 100 U group and a total of 100 treated patients after 1 year, at least 72 patients must be included in each Xeomin treatment group and 36 patients in the placebo group to fulfil the requirements set out in the ICH E1 guideline. The total sample size was thus required to be at least 180 patients o uSFR: Based on data from Chinnapongse *et al. (*2012) (NCT00515437), with an assumed drop-out rate of 5% up to Week 4 and a 2:2:1 randomisation ratio, an estimated number of 46 patients per Xeomin treatment group and 23 patients in the placebo group was to provide a 95% power to show a statistically significant difference between either of the Xeomin groups and placebo (2-sided Satterthwaite t-test, significance level α=0.05). The total sample size required was thus at least 115 patients o GICS: Based on data from Chinnapongse *et al. (*2012) (NCT00515437), with an assumed drop-out rate of 5% up to Week 4 and a 2:2:1 randomisation ratio, an estimated number of 20 patients per Xeomin treatment group and 10 patients in the placebo group was to provide 95% power to show a statistically significant difference between any of the Xeomin groups and placebo (2-sided Satterthwaite t-test, significance level α=0.05). The total sample size required was thus at least 50 patients • Thus, of these 3 criteria, safety required the greatest number of patients, so total sample size for the study was chosen to be N=180
Data management, patient withdrawals	Missing values of the efficacy variables were accounted for using the MMRM approach. In order to investigate the impact of missing values and different approaches for imputation, sensitivity analyses were performed using the baseline observation carried forward approach (BOCF, no effect) for uSFR, while imputing missing GICS entries at Week 4 as "no change" and without missing replacement. For this purpose, the MMRM model as described above was adapted as an analysis of covariance (ANCOVA) model using the SAS procedure

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	PROC MIXED but without visit*treatment as interaction and without visit as repeated factor

Abbreviations: ANCOVA: analysis of covariance; BOCF: baseline observation carried forward; DSFS: Drooling Severity and Frequency Scale; EP: extension period; GICS: Global Impression of Change Scale; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; LS-Means: least square means; MMRM: mixed model repeated measurement analysis; MP: main period; U: units; uSFR: unstimulated salivary flow rate.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

B.2.4.1 Patient disposition

A total of 216 patients were screened for eligibility into the SIAXI trial, of whom 184 patients were randomised (in a 2:2:1 ratio) and treated in the MP: 74 patients in each Xeomin dose group (75 U and 100 U) and 36 patients in the placebo group.[35] The trial was conducted across 23 sites in Germany and Poland. In Germany, 65 patients were screened at 12 sites; of these, 53 patients were randomised and treated at 11 sites. In Poland, 151 patients were screened and 131 patients were randomised and treated at 21 sites.[40] The SES-MP and the FAS comprised all 184 patients.[40]

Overall, 11 patients (6.0%) discontinued in the MP (Xeomin 100 U: N=2, Xeomin 75 U: N=5; placebo: N=4).[35] A summary of reasons for discontinuation is presented in Table 8. No patient stated lack of efficacy as the reason for discontinuation. A consort diagram of patient disposition is presented in Appendix L.

[redacted]

Table 8: Reasons for study discontinuation in the MP

	Xeomin 100 U	Xeomin 75 U	Placebo	Total
	N (%)	N (%)	N (%)	N (%)
Completed MP	72 (97.3)	69 (93.2)	32 (88.9)	173 (94.0)
Discontinued MP	2 (2.7)	5 (6.8)	4 (11.1)	11 (6.0)
Reason for discontinuation[a]				
AE(s)[b]	1 (1.4)	1 (1.4)	1 (2.8)	3 (1.6)
Withdrawal by patient	1 (1.4)	4 (5.4)	3 (8.3)	8 (4.3)
Physician decision	1 (1.4)	0 (0.0)	1 (2.8)	2 (1.1)
Lost to follow up	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.5)

100% base = N = number of patients randomised. [a]Multiple entries possible. [b]AEs were not treatment-related.
Abbreviations: AEs: adverse events; MP: main period.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

A total of 173 patients completed the MP and entered the EP (Xeomin 100 U: N=89; Xeomin 75 U: N=84). Altogether, these patients constituted the SES-EP. Overall, 22 patients (12.7%) discontinued the EP, with a higher proportion of patients in the 100 U group discontinuing than in the 75 U group (Xeomin 100 U: N=14, 15.7%; Xeomin 75 U: N=8, 9.5%).[40] A summary of reasons for discontinuation from the EP is presented in Table 9.[redacted]

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[redacted]

Table 9: Reasons for study discontinuation in the EP

	Xeomin 100 U	Xeomin 75 U	Total
	N (%)	N (%)	N (%)
Completed EP	75 (84.3)	76 (90.5)	151 (87.3)
Discontinued EP	14 (15.7)	8 (9.5)	22 (12.7)
Reason for discontinuation[a]			
Death	2 (2.2)	3 (3.6)	5 (2.9)
AE(s)	8 (9.0)	4 (4.8)	12 (6.9)
Lack of efficacy	1 (1.1)	0 (0.0)	1 (0.6)
Withdrawal by patient	8 (9.0)	4 (4.8)	12 (6.9)
Physician decision	2 (2.2)	0 (0.0)	2 (1.2)
Other	0 (0.0)	1 (1.2)	1 (0.6)

[a]Multiple entries possible.
Abbreviations: AEs: adverse events; EP: extension period.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

An overview of the quality assessment of the SIAXI trial is presented in Table 10. The quality assessment was performed based on the University of York Centre for Reviews and Dissemination (CRD) RCT checklist.[34]

Table 10: Quality assessment of the SIAXI trial

Study ID and publications	SIAXI (NCT02091739)[35-39]
Was the randomisation method adequate?	Unclear – no details were provided.
Was the allocation adequately concealed?	Not reported – no details were provided on allocation concealment.
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes – baseline demographics and disease characteristics were similar between treatment groups.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes – study described as double blind.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No – only two patients dropped out, and these were deemed to be unrelated to the study medication. Analyses were adjusted to exclude these patients from the final analyses.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No – all predefined outcomes were reported.
Did the analysis include an intention-to-treat analysis?	No – the full analysis set (FAS) was used, which was the subset of participants who were treated and had at least the baseline value of unstimulated salivary flow.

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Did the authors of the study publication declare any conflicts of interest?	Yes – authors declared the study was sponsored by Merz Pharmaceuticals GmbH, who developed the drug under investigation, and declared any other support that they received.

Abbreviations: FAS: full analysis set.

B.2.6 Clinical effectiveness results of the relevant trials

The anticipated licensed dose for Xeomin in this indication is 100 U. However, for completeness, the results for patients receiving 75 U Xeomin in the SIAXI trial have also been presented in this submission.

B.2.6.1 Main Period (MP)

In the MP, patients were randomised in a ratio of 2:2:1 into three treatment groups: two groups received active Xeomin treatment (75 U or 100 U, in a ratio of 1:1, respectively) and one group received placebo. The MP comprised one treatment cycle (16±2 weeks).

The co-primary endpoints of the SIAXI trial were change in unstimulated salivary flow rate (uSFR) from study baseline to Week 4 and patients' Global Impression of Change Scale (GICS) at Week 4.[35]

Change in unstimulated salivary flow rate (uSFR) – MP

uSFR was calculated via the swab method, whereby the weight increase of 4 absorbent rolls placed directly at the orifices of the salivary glands for 5 minutes was measured, and used to calculate the salivary flow rate in g/minute.[35] The procedure was repeated after 30 minutes and the average of the two results calculated.[35] Results for the change in uSFR are summarised in Table 10.

In the Xeomin 100 U group, treatment with Xeomin led to a statistically significant reduction in mean uSFR versus placebo. The LS-Mean change from baseline in the Xeomin 100 U group was -0.13 (standard error [SE]: 0.026) versus -0.04 (SE: 0.033) in the placebo group, hence the LS-Mean difference between the two groups was -0.09 (SE: 0.031) (p=0.004).

In the Xeomin 75 U group, treatment with Xeomin led to greater reduction in mean uSFR versus placebo. The LS-Mean change from baseline in the Xeomin 75 U group was -0.06 (SE: 0.027) versus -0.04 (SE: 0.033) in the placebo group. The LS-Mean difference between the Xeomin 75 U group and placebo group was -0.02 (SE: 0.030) (p=0.542). Whilst this reduction did not represent a statistically significant difference compared to placebo at Week 4, statistical significance was reached by Week 8.

Significantly greater reductions in mean uSFR were observed for both Xeomin treatment groups at Weeks 8 and 12, and were maintained to Week 16, as shown in Table 11 and Figure 5.[35]

Table 11: Change in uSFR from baseline to Week 4 – MP (FAS)

	N	Xeomin 100 U	N	Xeomin 75 U	N	Placebo
Baseline						
Mean (SD)	74	0.40 (0.27)	74	0.42 (0.28)	36	0.38 (0.23)
Week 4						
Mean (SD)	73	0.27 (0.18)	73	0.36 (0.25)	36	0.36 (0.19)

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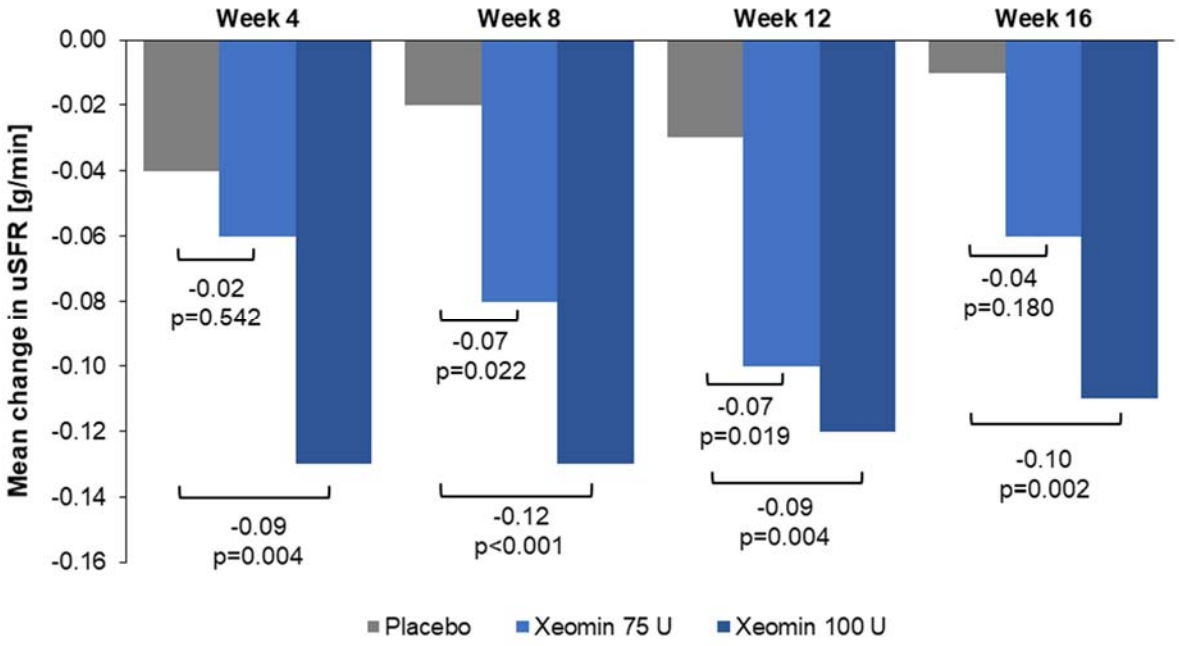
Mean change from baseline to Week 4						
Mean change (SD)	73	-0.12 (0.21)	73	-0.07 (0.15)	36	-0.03 (0.21)
LS-Mean change (SE) (95% CI)	73	-0.13 (0.026) (-0.18; -0.08)	73	-0.06 (0.027) (-0.11; -0.01)	36	-0.04 (0.033) (-0.11; 0.03)
LS-Mean change difference versus placebo (95% CI)	73	-0.09 (0.031) (-0.15; -0.03)	73	-0.02 (0.030) (-0.08; 0.04)	-	-
p-value (versus placebo)		0.004		0.542	-	-

uSFR is given in g/min. uSFR was analysed via the MMRM approach. LS-Means are from the model with treatment, country, gender, use of ultrasound and aetiology included as (fixed) factors and uSFR at baseline included as covariate. For MMRM visit*treatment is interaction term and visit is repeated factor.
Abbreviations: CI: confidence interval; FAS: full analysis set; LS: least squares; MP: main period; MMRM: mixed model repeated measurement analysis; MP: main period; SD: standard deviation; SE: standard error; U: units; uSFR: unstimulated salivary flow rate.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Figure 5: LS-Mean change in uSFR from study baseline to Weeks 4, 8, 12 and 16 – MP (FAS)



uSFR is given in g/min. uSFR was analysed via the MMRM approach. p-values were calculated for the LS-Mean difference between each treatment group vs placebo. LS-Means are from the model with treatment, country, gender, use of ultrasound and aetiology included as (fixed) factors and uSFR at baseline included as covariate. For MMRM visit*treatment is interaction term and visit is repeated factor.
Abbreviations: FAS: full analysis set; LS: least squares; MP: main period; MMRM: mixed model repeated measurement analysis; MP: main period; U: units; uSFR: unstimulated salivary flow rate.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Patient's Global Impression of Change Scale (GICS) Results – MP

The Global Impression of Change Scale is a self-administered questionnaire in which patients (or carers) report their impression of change with respect to baseline using 7-point Likert scale that ranges from -3 (very much worse) to +3 (very much improved). The question for the patient was: 'Compared to how you were doing just before the last injection into your salivary gland, what is your overall impression of how you are functioning now as a result of this treatment?' If the patient was not able to answer this question even with assistance, then the carer's rating was

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analysed instead. However, carer´s GICS was used only GICS for four patients at some telephone visits, as all patients rated GICS themselves at Week 4 and all other study visits.

A summary of the GICS scores at Week 4 are presented in Table 12. For the Xeomin 100 U group, the LS-Mean GICS score at Week 4 was 1.25 (SE: 0.144) compared with 0.67 (SE: 0.186) in the placebo group. The LS-Mean difference between the Xeomin 100 U group and placebo group was 0.58 (SE: 0.183), representing a statistically significant difference in GICS scores between these groups (p=0.002).[40]

For the Xeomin 75 U group, the LS-Mean GICS score at Week 4 was 1.02 (SE: 0.148), compared with 0.67 (SE: 0.186) in the placebo group. The LS-Mean difference in GICS score between the Xeomin 75 U group and placebo group was 0.35 (SE: 0.181) (p=0.055).[40]

Both the Xeomin 100 U and Xeomin 75 U treatment groups showed improvements in symptoms (positive GICS scores) at Week 8 and Week 12, and these improvements were maintained to Week 16, as shown in Figure 6.[34] Both Xeomin treatment groups had statistically significant higher GICS scores compared to placebo at Week 8 and Week 12 (p<0.05 for both groups).[33]

Table 12: Patient's GICS at Week 4 – MP (FAS)

	N	Xeomin 100 U	N	Xeomin 75 U	N	Placebo
Mean score at Week 4 (SD)	73	1.04 (1.03)	73	0.84 (0.78)	36	0.47 (0.84)
LS-Mean (SE) (95% CI)	74	1.25 (0.144) (0.97; 1.53)	74	1.02 (0.148) (0.73; 1.31)	36	0.67 (0.186) (0.30; 1.04)
LS-Mean difference versus placebo (SE) (95% CI)	74	0.58 (0.183) (0.22; 0.94)	74	0.35 (0.181) (-0.01; 0.71)	-	-
p-value		0.002		0.055	-	-

GICS: -3 = Very much worse function, -2 = Much worse function, -1 = Minimally worse function, 0 = No change in function, 1 = Minimally improved function, 2 = Much improved function, 3 = Very much improved function. Carer's GICS entry was used if patient's GICS was not available. GICS scores were analysed via the MMRM approach. LS-Means are from model with treatment, country, gender, use of ultrasound and aetiology included as (fixed) factors and DSFS sum score at baseline included as covariate. For MMRM visit*treatment is interaction term and visit is repeated factor.
Abbreviations: CI: confidence interval; FAS: full analysis set; GICS: global impression of change scale; LS: least squares; MMRM: mixed model repeated measurement analysis; MP: main period; SD: standard deviation; SE: standard error; U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

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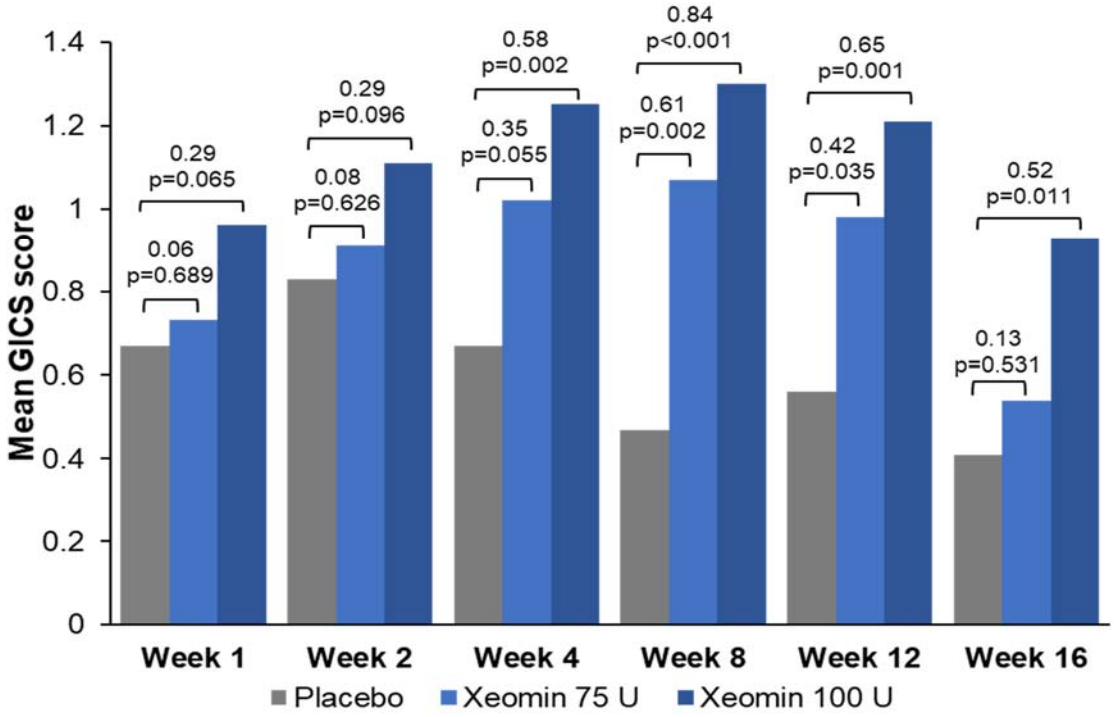
Figure 6: Patient's GICS at Week 1, Week 2, Week 4, Week 8, Week 12 and Week 16 – MP (FAS)



GICS: -3 = Very much worse function, -2 = Much worse function, -1 = Minimally worse function, 0 = No change in function, 1 = Minimally improved function, 2 = Much improved function, 3 = Very much improved function
Carer's GICS entry was used if patient's GICS was not available. GICS scores were analysed via the MMRM approach. LS-Means are from model with treatment, country, gender, use of ultrasound and etiology included as (fixed) factors and DSFS sum score at baseline included as covariate. For MMRM visit*treatment is interaction term and visit is repeated factor.
Abbreviations: CI: confidence interval; FAS: full analysis set; GICS: global impression of change scale; LS: least squares; MP: main period; SD: standard deviation; SE: standard error; U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Proportion of responders based on GICS – MP

The proportion of responders, defined as having a GICS score of ≥1, [redacted] A summary of the proportion of responders is presented in Table 13.

Table 13: Proportion of responders based on patient's GICS entry at Weeks 1, 2, 4, 8, 12 and 16 – MP (FAS)

	Xeomin 100 U (N=74)		Xeomin 75 U (N=74)		Placebo (N=36)
	n/N (%)	p-value[a]	n/N (%)	p-value[a]	n/N (%)
Week 1	[redacted]				
Week 2					
Week 4					
Week 8					
Week 12					

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Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]Fisher's exact test was used to generate p values for the comparison of each Xeomin treatment arm with placebo. Responder: GICS entry of at least +1 (minimally improved function). Carer's GICS entry is used if patient's GICS is not available. For worst case imputation a patient with missing values is considered as non-responder. n/N = Number of patients showing response at the visit.
Abbreviations: FAS: full analysis set; GICS: global impression of change scale; MP: main period; U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Carer's Global Impression of Change Scale (GICS) – MP

Analogous to the patient's GICS, carers completed a self-administered questionnaire in which they reported their impression of the patient's change with respect to baseline. The question for the caregiver was: "Compared to how the patient was doing just before the last injection into his/her salivary gland, what is your overall impression of how he/she is functioning now as a result of this treatment?".

[redacted]
14 [redacted]

Table 14: Carer's GICS entry at Weeks 1, 2, 4, 8, 12 and 16 – MP (FAS)

	Xeomin 100 U (N=74)		Xeomin 75 U (N=74)		Placebo (N=36)	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Week 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

GICS: -3 = Very much worse function, -2 = Much worse function, -1 = Minimally worse function, 0 = No change in function, 1 = Minimally improved function, 2 = Much improved function, 3 = Very much improved function.
Abbreviations: FAS: full analysis set; GICS: global impression of change scale; MP: main period; SD: standard deviation; U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Drooling Severity and Frequency Scale (DSFS) – MP

The drooling severity and frequency subscale (DSFS) consists of 2 subscales: a 4-point Likert scale for 'drooling frequency', ranging from 1 (never) to 4 (constantly), and a 5-point Likert scale for 'drooling severity', ranging from 1 (dry) to 5 (profuse). The DSFS is the sum score of the two subscales, with a maximum (worst) score of 9. The time period used for each evaluation was "over the past week".

At baseline, the mean DSFS sum score was 6.78 for the Xeomin 100 U group, 6.88 for the Xeomin 75 U group, and 6.97 for the placebo group. Patients in both Xeomin treatment groups had significantly greater improvements from baseline in the DSFS sum score at Week 4, Week 8 and Week 12 compared to placebo (p-values <0.05). A summary of change from baseline in DSFS sum score at Weeks 4, 8, 12 and 16 is shown in Figure 7.

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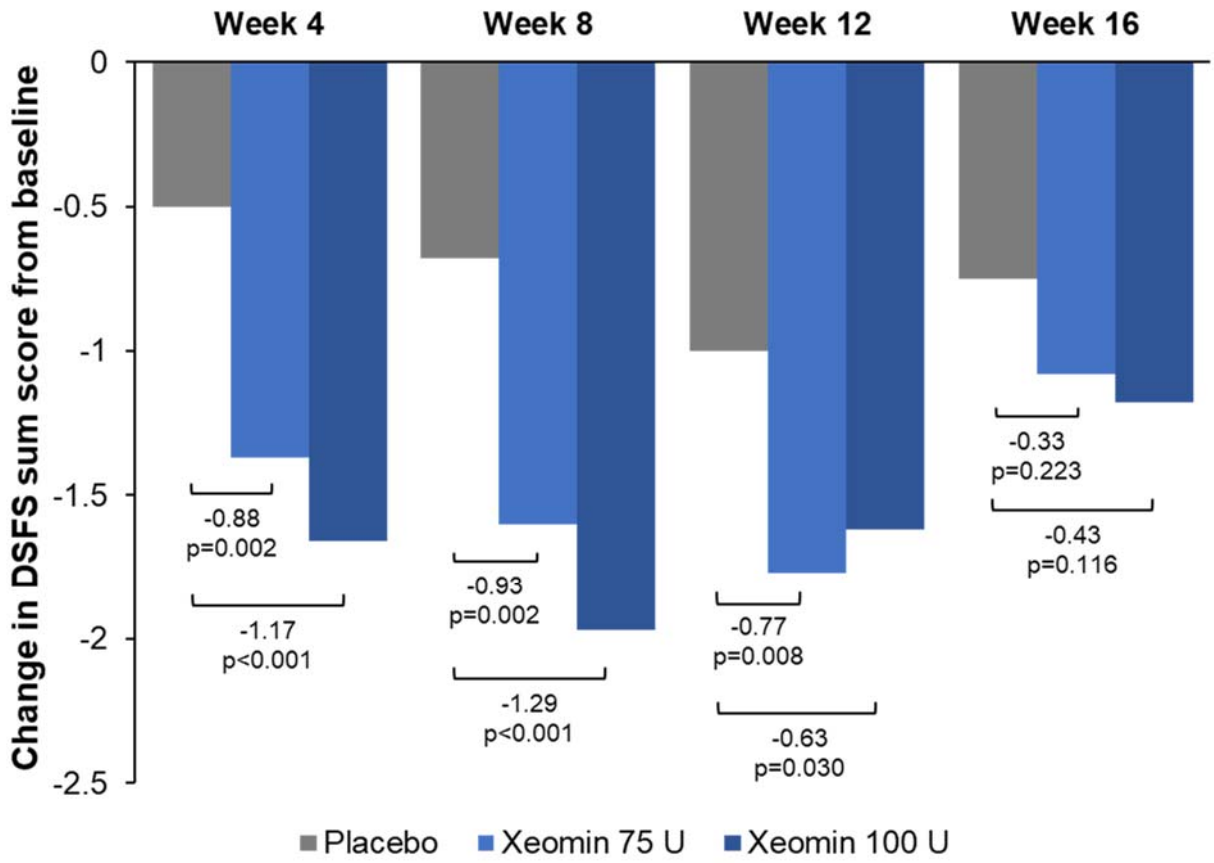
Figure 7: Change in DSFS sum score from study baseline to Weeks 4, 8, 12, and 16 – MP (FAS)



DSFS scores was analysed via the MMRM approach. LS-Means are from model with treatment, country, gender, use of ultrasound and aetiology included as (fixed) factors and DSFS sum score at baseline included as covariate. For MMRM visit*treatment is interaction term and visit is repeated factor. n = number of subjects who were used in the corresponding analysis and who were included in the respective treatment group and analysis set.
DSFS sum score ranges from 2 (best) to 9 (worst).
Abbreviations: CI: confidence interval; FAS: full analysis set; GICS: global impression of change scale; LS: least squares; MP: main period; SD: standard deviation; SE: standard error; U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Modified Radboud Oral Motor Inventory for Parkinson's Disease (mROMP) – MP

The modified Radbound Oral Motor Inventory of Parkinson's Disease (mROMP) is a 24-item questionnaire where each item is measured on a 5-point Likert scale. The mROMP consists of three parts: I = speech, II = swallowing symptoms and III = drooling. Parts I and III were administered as efficacy assessments. Part II was administered as a safety assessment (see Section B.2.10.1).

mROMP speech symptoms scores improved for all treatment groups from study baseline to all post-baseline visits of the MP.

[redacted] Table 15 [redacted] Table 16 [redacted].

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Table 15: Change in mROMP speech symptoms from study baseline to Weeks 4, 8, 12 and 16 – MP (FAS)

	Xeomin 100 U		Xeomin 75 U		Placebo	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Score ranges from 8 (best) to 40 (worst).
Abbreviations: FAS: full analysis set; MP: main period; mROMP: modified Radboud oral motor inventory for Parkinson's disease; SD: standard deviation; U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Table 16: Change in mROMP drooling scores from study baseline to Weeks 4, 8, 12 and 16 – MP (FAS)

	Xeomin 100 U		Xeomin 75 U		Placebo	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Score ranges from 9 (best) to 45 (worst).
Abbreviations: FAS: full analysis set; MP: main period; mROMP: modified Radboud oral motor inventory for Parkinson's disease; SD: standard deviation; U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

B.2.6.2 Extension Period (EP)

Following completion of the MP, patients who were eligible entered the EP. All patients who entered the EP received Xeomin but were blinded with respect to dose level (75 U or 100 U). The EP comprised three treatment cycles (each 16±2 weeks) and concluded with an end-of-study examination at the end of the final cycle.[35]

Change in unstimulated salivary flow rate (uSFR) – EP

Mean uSFR values were progressively lower at each cycle baseline in both Xeomin treatment groups, and remained numerically higher in the Xeomin 75 U group than the Xeomin 100 U group at each cycle baseline [redacted]

Improvements in uSFR from study baseline to each visit in the EP were observed in both Xeomin treatment groups, as shown in Table 17 and improvements were also observed from each cycle baseline to the assessment visits and end-of-cycle visits for each cycle.[40]

[redacted] as shown in Figure 8. [redacted]

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Table 17: Change in uSFR from study baseline to all visits in the EP – EP (SES-EP)

	Xeomin 100 U		Xeomin 75 U	
	N	Mean (SD)	N	Mean (SD)
Change from study baseline in Cycle 2				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Change from study baseline in Cycle 3				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Change from study baseline in Cycle 4				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Change from study baseline to the end of the study	[redacted]	[redacted]	[redacted]	[redacted]

uSFR is given in g/min. Includes all patients in the EP irrespective of treatment received in the MP.
Abbreviations: EP: extension period; SD: standard deviation; SES-EP: safety evaluation set (extension period); uSFR: unstimulated salivary flow rate; U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Figure 8: Change in uSFR across the study EP – (SES-EP)

Abbreviations: EP: extension period; SES-EP: safety evaluation set (extension period); uSFR: unstimulated salivary flow rate; U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

The overall Xeomin 100 U and Xeomin 75 U treatment groups in the EP included patients who had already received Xeomin in the MP and patients who were receiving Xeomin for the first time in the EP (i.e. had received placebo in the MP). As there may have been differences in the

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treatment effect between these two patient groups, an analysis was conducted that included only those patients who had received Xeomin in the MP. Results from this analysis were consistent with the overall analysis and are not presented here (full results can be found in the SIAXI CSR).

Patient's Global Impression of Change Scale (GICS) – EP

A summary of patient's GICS entries in the EP is presented in Table 18.

[redacted] The question for the GICS always referred to changes compared to the status just before the last injection.[40]

Table 18: Patient's GICS entry at all assessment visits in the EP, at the end-of-study visit and at all telephone contacts – EP (SES-EP)

	Xeomin 100 U		Xeomin 75 U	
	N	Mean (SD)	N	Mean (SD)
Cycle 2				
Week 1 (TC)	[redacted]	[redacted]	[redacted]	[redacted]
Week 2 (TC)	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 8 (TC)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3				
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 8 (TC)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4				
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 8 (TC)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
End of study	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EP: extension period; GICS: global impression of change scale; SD: standard deviation; SES-EP: safety evaluation set (extension period); TC: telephone contact; U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Proportion of responders based on GICS – EP

A summary of the number of responders based on patient's GICS entries in the EP is presented in Table 19.

[redacted]

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Table 19: Number of responders based on the patient's GICS entry at all assessment visits in the EP, at the end-of-study visit and at all telephone contacts – EP (SES-EP)

	Xeomin 100 U		Xeomin 75 U	
	n/N	Responders (%)	n/N	Responders (%)
Cycle 2				
Week 1 (TC)	[redacted]	[redacted]	[redacted]	[redacted]
Week 2 (TC)	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 8 (TC)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3				
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 8 (TC)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4				
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 8 (TC)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
End of study	[redacted]	[redacted]	[redacted]	[redacted]

Responder: GICS entry of at least +1 (Minimally improved function). n/N = Number of patients treated in respective cycle and assigned to respective treatment group and with the response or non-response in the subgroup at the visit/Number of patients treated in respective cycle and assigned to respective treatment group. Carer's GICS entry was used if patient's GICS was not available. Randomised treatment group was used.
Abbreviations: EP: extension period; GICS: global impression of change scale; SES-EP: safety evaluation set (extension period); TC: telephone contact; U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Carer's Global Impression of Change Scale (GICS) – EP

A summary of the carer's GICS results at all assessment visits in the EP, at the end-of-study visit and at all telephone contacts are presented in Table 20.

[redacted] The question for the GICS always referred to changes compared to the status just before the last injection.[40]

Table 20: Carer's GICS entry at all assessment visits in the EP, at the end-of-study visit and at all telephone contacts – EP (SES-EP)

	Xeomin 100 U		Xeomin 75 U	
	N	Mean (SD)	N	Mean (SD)
Cycle 2				
Week 1 (TC)	[redacted]	[redacted]	[redacted]	[redacted]
Week 2 (TC)	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 8 (TC)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3				

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Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 8 (TC)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4				
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 8 (TC)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
End of study	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EP: extension period; GICS: global impression of change scale; SD: standard deviation; SES-EP: safety evaluation set (extension period); TC: telephone contact; U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Drooling Severity and Frequency Scale (DSFS) – EP

The DSFS sum score improved from study baseline to each Week 4 visit of the individual injection cycles, as demonstrated in Table 21.

[redacted]

Table 21: Change in DSFS sum score from study baseline to all assessment visits in the EP (SES-EP)

	Xeomin 100 U		Xeomin 75 U	
	N	Mean (SD)	N	Mean (SD)
Change from study baseline to:				
Cycle 2 Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Week 4	[redacted]	[redacted]	[redacted]	[redacted]

DSFS sum score ranges from 2 (best) to 9 (worst).
Randomized treatment group was used.
Abbreviations: EP: extension period; DSFS: drooling severity and frequency score; SD: standard deviation; SES-EP: safety evaluation set (extension period); U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Modified Radboud Oral Motor Inventory for Parkinson's Disease (mROMP) – EP

[redacted]Table 22[redacted]Table 23[redacted]

Table 22: Change in mROMP Speech Symptoms from study baseline to all assessment visits in the EP (SES-EP)

	Xeomin 100 U		Xeomin 75 U	
	N	Mean (SD)	N	Mean (SD)
Change from study baseline to:				

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Cycle 2 Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Week 4	[redacted]	[redacted]	[redacted]	[redacted]

Score ranges from 8 (best) to 40 (worst).
Abbreviations: EP: extension period; mROMP: modified Radboud oral motor inventory for Parkinson's disease; SD: standard deviation; SES-EP: safety evaluation set (extension period); U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Table 23: Change in mROMP drooling scores from study baseline to all assessment visits in the EP (SES-EP)

	Xeomin 100 U		Xeomin 75 U	
	N	Mean (SD)	N	Mean (SD)
Change from study baseline to:				
Cycle 2 Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Week 4	[redacted]	[redacted]	[redacted]	[redacted]

Score ranges from 9 (best) to 45 (worst).
Abbreviations: EP: extension period; mROMP: modified Radboud oral motor inventory for Parkinson's disease; SD: standard deviation; SES-EP: safety evaluation set (extension period); U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

B.2.6.3 Health-related quality of life

EQ-5D-3L

EQ-5D is a standardised measure of health status developed by the EuroQol Group. The three-level version (EQ-5D-3L) includes the EQ VAS, which records the patient's self-rated health status on a vertical visual analogue scale ranging from "best imaginable health state" to "worst imaginable health state", and the EQ-5D descriptive system which asks respondents to rate the level of difficult they experience with self-care, usual activities, pain/discomfort and anxiety/depression as "no problems", "some problems", or "extreme problems". Changes in EQ-5D-3L single items and visual analogue scale (VAS) were measured every four weeks in the MP and every 16 weeks in the EP. Overall, no clinically relevant shifts in the EQ-5D-3L single line items were observed in the MP or EP.

[redacted] Table 24. [redacted], as summarised in Table 25.[40]

Table 24: Change in EQ-VAS from baseline to Weeks 4, 8, 12 and 16 of the MP (FAS)

	Xeomin 100 U		Xeomin 75 U		Placebo	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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VAS ranges from 0 (= worst imaginable health state) to 100 (= best imaginable health state).
Abbreviations: FAS: full analysis set; MP: main period; SD: standard deviation; U: units; VAS: visual analogue score.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Table 25: Change in EQ VAS from study baseline to all assessment visits in the EP (SES-EP)

	Xeomin 100 U		Xeomin 75 U	
	N	Mean (SD)	N	Mean (SD)
Cycle 2 Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Week 4	[redacted]	[redacted]	[redacted]	[redacted]

VAS ranges from 0 (= worst imaginable health state) to 100 (= best imaginable health state). Randomized treatment group was used.
Abbreviations: EP: extension period; SD: standard deviation; SES-EP; safety evaluation set (extension period); U: units; VAS: visual analogue score.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

B.2.7 Subgroup analysis

B.2.7.1 Main Period

Subgroup analyses were performed for uSFR, GICS and DSFS in the MP by aetiology of sialorrhoea, method of administration, gender, and country. Please note that due to the low number of patients in the subgroup with sialorrhoea after traumatic brain injury, no reliable conclusion can be made for this subgroup.[40] Subgroup analyses for the coprimary endpoints of change from baseline to Week 4 in uSFR and patients' GICS are presented below. For details of further subgroup analyses of the EP, please refer to Appendix E.

Change in unstimulated salivary flow rate (uSFR) – MP

Subgroup analyses based on the mean changes from study baseline to week 4 for uSFR are presented in Table 26.[40]

[redacted]

Table 26: Subgroup analysis of change from baseline to Week 4 in uSFR – MP (FAS)

	Xeomin 100 U		Xeomin 75 U		Placebo	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Aetiology of sialorrhoea						
Sialorrhoea associated with Parkinson's disease or atypical parkinsonism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sialorrhoea after stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sialorrhoea after traumatic brain injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Method of administration						
Ultrasound guidance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anatomic landmarks guided	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Country						
Germany	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Poland	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender						
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

uSFR is given in g/min
Abbreviations: FAS: full analysis set; MP: main period SD: standard deviation; uSFR: unstimulated salivary flow rate.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Patient's Global Impression of Change Scale (GICS) – MP

Subgroup analyses based on the mean patient's GICS at Week 4 are presented in Table 27.

[redacted]

[redacted]

Table 27: Subgroup analysis of change from baseline to week 4 in patient's GICS – MP (FAS)

	Xeomin 100 U		Xeomin 75 U		Placebo	
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Aetiology of sialorrhoea						
Sialorrhoea associated with Parkinson's disease or atypical parkinsonism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sialorrhoea after stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sialorrhoea after traumatic brain injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Method of administration						
Ultrasound guidance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anatomic landmarks guided	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Country						
Germany	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Poland	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender						
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

GICS: -3 = Very much worse function, -2 = Much worse function, -1 = Minimally worse function, 0 = No change in function, 1 = Minimally improved function, 2 = Much improved function, 3 = Very much improved function. Carer's GICS entry was used if patient's GICS was not available.
Abbreviations: FAS: full analysis set; GICS: global impression of change scale; Sd: standard deviation.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Change in drooling severity and frequency scale sum score – MP

Subgroup analyses of mean change in DSFS sum score from study baseline to Week 4 are presented in Table 28.

[redacted]

Table 28: Subgroup analysis of change in DSFS sum score from study baseline to Week 4– MP (FAS)

	Xeomin 100 U		Xeomin 75 U		Placebo	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Aetiology of sialorrhoea						
Sialorrhoea associated with Parkinson's disease or atypical parkinsonism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sialorrhoea after stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sialorrhoea after traumatic brain injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Method of administration						
Ultrasound guidance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anatomic landmarks guided	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Country						
Germany	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Poland	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender						
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Female	[redacted]					

Abbreviations: FAS: full analysis set; GICS: global impression of change scale; SD: standard deviation.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

B.2.8 Meta-analysis

N/A – no meta-analysis was performed as part of this submission. As described in Section B.2.2, the small crossover study identified for Xeomin was deemed to have too small a sample size to warrant a pooling of data from the SIAXI trial.

B.2.9 Indirect and mixed treatment comparisons

The search strategies employed by the SLR described in Appendix D were used to identify clinical evidence for the relevant comparators: oral glycopyrronium bromide and SoC. The SLR included all studies investigating anticholinergic therapies rather than glycopyrronium bromide alone. In total, 15 RCTs reported in 18 records were identified for anticholinergic therapies or SoC from the SLR (see Appendix D). No studies were identified directly comparing Xeomin to any anticholinergic therapies. All the trials identified compared active treatment to placebo; therefore, a feasibility assessment was undertaken to establish whether a viable indirect treatment comparison (ITC) could be undertaken using the RCT evidence identified by the SLR.

Following a feasibility assessment of the identified evidence, it was determined that differences in patient populations, outcome measures, as well as study design, precluded the conduct of any robust ITCs between Xeomin and any anticholinergic therapies. The reasons for this are detailed below.

B.2.9.1 Heterogeneity in patient population

An overview of patient population characteristics from the included trials of the SLR is given in Table 29. Reporting of baseline characteristics in general among the included studies was poor, with few studies providing information beyond age and severity of sialorrhoea.

Severity and onset of sialorrhoea

Most studies used a validated scale to measure the severity of sialorrhoea. However, the choice of scale used to screen patients at recruitment varied from study-to-study, ranging from sialorrhoea-tailored scales to disease-specific saliva subscales. This introduces difficulty in assessing whether the severity of sialorrhoea was comparable among the study populations. For example, SIAXI used the Drooling Severity and Frequency Scale (DSFS), in combination with the disease-specific modified Radboud Oral Motor Inventory for Parkinson's disease (mROMP) drooling subscale[35-39] Narayanaswami 2016 used the Functional Oral Intake Scale (FOIS),[41, 42] whereas Odachi 2017 utilised the disease-specific total and saliva subscale score of the revised ALS Functional Rating Scale (ALSFRS-R).[43] Perez-Lloret 2011 used the disease-specific Sialorrhoea Clinical Scale for PD (SCS-PD),[44, 45] and Thomsen 2007 used the salivation subdomain of the disease-specific Unified Parkinson's disease rating scale (UPDRS).[46] Finally, Arbouw 2010 used a custom sialorrhoea scoring scale;[47] Brodtkorb 1988 and Mato 2010 did not use any scale, instead describing drooling as either constant or persistent.[31, 47]

The onset period of sialorrhoea was also not defined in all studies, which may also have an effect on the overall severity of sialorrhoea and therefore observed treatment effects versus studies that did not use sialorrhoea onset as an inclusion criterion. The lack of concordance among studies' definitions of sialorrhoea, which could otherwise have been used to reconcile the

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differences in patients' underlying neurological conditions, introduces further heterogeneity in combining these studies for an ITC.

Age of patients at baseline and inclusion of paediatric patients

The majority of studies either recruited adults exclusively or patients with neurological conditions with late-age onset (there was no evidence in the captured studies to suggest early-onset Parkinson's disease patients were included), with mean ages ranging from 64.7 to 71.6 years in these studies. Exceptions included Brodtkorb 1988 and Mato 2010, which enrolled patients who were younger (mean 34 and 30 years, respectively), likely down to differences in underlying neurological conditions.[31, 48] Mato 2010 recruited at least one paediatric patient (inferred from the age range of participants [12–58 years]). There was no evidence to suggest Mato 2010 adjusted treatment dosing or frequency to account for any paediatric patients, whose response and tolerability to treatment may differ from the adult population.[31] This may have implications for the treatment efficacy reported in this trial and, in turn, when analysed in an ITC.

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Table 29: Summary of populations across studies

Study	No. of patients	Mean age (SD), years	Underlying condition	Duration of underlying condition	Sialorrhoea scoring	UPDRS III Score rating	Onset period of sialorrhoea
SIAXI (NCT02091739)[35-39]	184	65.2 (11.4)	Parkinson's Disease or atypical Parkinsonism, stroke or traumatic brain injury	Documented diagnosis ≥6 months prior to screening	• A DSFS sum score of at least 6 points and • A score of at least 2 points for each item of the DSFS and • A score of at least 3 points on the mROMP, Section 'III Drooling', Item A	Mean 2.1	At least 3 months before screening
Narayanaswami 2016 (NCT01653132)[41, 42]	10	Placebo first: 64.7 (4.8) Xeomin first: 70.8 (12.3)	• Parkinson's Disease/Parkinsonism • Multiple Systems Atrophy (MSA) • Progressive Supranuclear Palsy (PSP)	NR	Swallowing function based on Functional Oral Intake Scale (FOIS) of 5 or greater	Mean 7 (pts randomised to placebo first) Mean 9 (pts randomised to study drug first)	NR
Bai 2006[49]	20	43.8 (9.9)	Schizophrenia	NR	Diameter of nocturnal saliva-wetted surface >10 cm	NR	NR
Brodtkorb 1988[48]	18	40 (NR)	• Down's Syndrome (n=3) • Cerebral Palsy (n=11) • Parkinson's disease	NR	NR	NR	NR

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Study	No. of patients	Mean age (SD), years	Underlying condition	Duration of underlying condition	Sialorrhoea scoring	UPDRS III Score rating	Onset period of sialorrhoea
			(n=1)[a]				
Colen-De 2015[50c]	10	NR Range: 18-65 years	Psychiatric patients	NR	NR	NR	NR
De Simone 2006[51]	22	NR Median: 66	Upper digestive cancer	NR	Score >30 on the VAS	NR	NR
Kreinin 2006[52]	20	NR	Schizophrenia	NR	Score ≥2 on the Nocturnal Hypersalivation Rating Scale (NHRS)	NR	NR
Kreinin 2016[53]	58	40.3 (11.9)	• Schizophrenia • Schizoaffective disorder	Mean 18.0 years	Score ≥2 on the NHRS	NR	NR
Liang 2010[54]	13	Biperiden first: 47.0 (9.0) Glycopyrrolate first: 46.0 (6.6)	Schizophrenia	Biperiden first: 23.3 years Glycopyrrolate: 23.4 years	Score ≥4 on the Drooling Rating Scale (DRS)	NR	NR
Man 2017[55]	Double-blinded: 32 Double Blinded and Open Label: 23	Double-blinded: 38.9 (11.2) Double Blinded and Open Label: 39.2 (12.1)	Psychiatric disorder	NR	Score ≥2 on the Patient Global Impression of Severity (PGI-S) scale	NR	NR
Mato 2010[31]	30	30.0 (14)	• Cerebral Palsy (n=11) • Epilepsy (n=5) • Autism (n=4) • Down's Syndrome (n=3) • Rare disorders (n=3)[b]	NR	NR	NR	NR

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Study	No. of patients	Mean age (SD), years	Underlying condition	Duration of underlying condition	Sialorrhoea scoring	UPDRS III Score rating	Onset period of sialorrhoea
Odachi 2017[43, 56]	10	71.6 (NR)	Amyotrophic lateral sclerosis (ALS) (n=10)	Mean 9.36 years	• ALSFRS-R (total) • ALSFRS-R (saliva)	NR	NR
Arbouw 2010[47]	25	70.0 (7.8)	Parkinson's disease	Mean 10.2 years	Score ≥5 on the sialorrhoea scoring scale	Mean 37.9	NR
Sockalingam 2009[57]	20	Ipratropium group: 40.0 (12.0) Placebo group: 38.8 (7.4)	• Schizophrenia • Schizoaffective disorder	NR	Score ≥2 on the Toronto Nocturnal Hypersalivation Scale (TNHS)	NR	NR
Takeuchi 2017[58]	20	NR (20.0 to 65.0 years)	• Schizophrenia (n=10) • Healthy adult men (n=10)	NR	NR	NR	NR
Thomsen 2007 (NCT00296946)[46]	17	70.0 (NR)	Parkinson's disease	Mean 10.8	Salivation score ≥2 on the UPDRS scale	Mean 27	NR
Perez-Lloret 2011 (NCT00761137) [44, 45, 59]	12	67.0 (12)	Parkinson's disease	Median 8 years	Salivation score rating on the SCS-PD scale score≥3	NR	At least 1 month before screening

[a]The underlying cause for three of the patients was not defined. [b]Total number of underlying neurological conditions sums to 26 as four patients dropped out. cUnable to obtain full text of Colen-De (2015).[50]

Abbreviations: ALSFRS-R: ALS functional rating scale; DSFS: drooling severity and frequency scale; mROMP: modified Radboud Oral Motor Inventory for Parkinson's disease; SCS-PD: Sialorrhoea Clinical Scale for PD; SD: standard deviation; UPDRS: Unified Parkinson's disease rating scale; FOIS: Functional Oral Intake Scale; NHRS: Nocturnal Hypersalivation Rating Scale; DRS: Drooling Rating Scale; PGI-S: Patient Global Impression of Severity; TNHS: Toronto Nocturnal Hypersalivation Scale; NR: not recorded; pts: patients; NA: not available.

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B.2.9.2 Heterogeneity in study design

All studies identified were randomised, placebo-controlled trials, as per the eligibility criteria for the review; however, all of the trials employed a cross-over design. In combination with uncertainty surrounding how these crossover trials were designed and conducted, this may introduce the following issues:

- Whilst a washout period was employed between treatment periods (7 days across trials, with the exception of Brodtkorb 1988 and Narayanaswami 2016, which used 4-day and 4-week periods, respectively),[41, 42, 48] it is possible that patients assigned to the active intervention first may still be subject to residual effects following the washout period, potentially confounding any efficacy or safety analyses in the following treatment period(s) (carry-over effects)
- Only two studies (Odachi 2017, Narayanaswami 2016) justified the length of their washout period; Narayanaswami 2016 adjusted its crossover length depending on the weight of saliva after a 4-week washout versus baseline levels in order to minimise carry-over effects.[41, 42, 48] Odachi 2017 was based on the timeframes used in Brodtkorb 1988 and Mato 2010, which also investigated scopolamine.[43] It is therefore unclear across the majority of trials captured whether the washout period used was appropriate and whether such carry-over effects were minimised
- If patients experience or perceive a more pronounced effect (positive or negative) in the first treatment period, this may confound efficacy or safety measurements through modification of patient sensitivity in subsequent periods

The duration of studies was also similarly heterogeneous, ranging from as little as 14 days to 8 months (when considering main treatment phase length only), with shorter (3–5 week) timeframes more common. The implications of this are discussed in greater detail in Section B.2.9.3. Trials that run over longer periods of time are likely to experience more discontinuations and see the emergence of adverse events associated with long-term treatment.[35-39, 41, 42] Combining data from interventions collected over different time periods is likely to bias analyses, for example by overestimating efficacy or underestimating the safety profile of a given intervention.

B.2.9.3 Heterogeneity in efficacy and safety outcomes

Timepoints

There was considerable heterogeneity in the timepoints defined to measure efficacy and safety. As discussed in Section **Error! Reference source not found.**, these ranged from minutes (Perez-Lloret 2011) to months (SIAXI, Narayanaswami 2016) which would create difficulties in comparing treatments at uniform timepoints.[35-39, 41, 42, 44, 46]

Efficacy outcomes

A summary of the efficacy outcomes reported in the captured trials is given in Table 30.

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Table 30: Summary in efficacy outcomes

Primary Outcome	Unstimulated salivary flow (g/min); saliva weight/volume (g)				Global Impression of Change (-3 to +3)					Change in drooling severity[a]						
Timepoint (weeks)	1	2	4	5	1	2	4	8	12	1	2	3	4	5	7	8
Xeomin																
SIAXI (NCT02091739)[35-39]	–	–	✓	–	–	–	✓	–	–	–	–	–	✓	–	–	–
Narayanaswami 2016 (NCT01653132)[41, 42]	–	–	✓	–	–	–	–	–	–	–	–	–	–	–	–	–
Glycopyrrolate (glycopyrronium bromide)																
Arbouw 2010[47]	–	–	–	–	–	–	–	–	–	✓[b]	✓[b]	–	✓[b]	–	–	–
Colen-De 2015[50c]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Man 2017[55]	–	–	–	–	✓	–	–	–	–	–	–	–	–	–	–	–
Scopolamine																
Brodtkorb 1988[48]	–	–	–	–	–	–	–	–	–	✓	–	–	–	–	–	–
Mato 2010[31]	–	–	–	–	–	–	–	–	–	✓	✓	–	–	–	–	–
Takeuchi 2017[58]	✓	✓	✓	✓	–	–	–	–	–	✓	✓	✓	✓	✓	–	–
Hyoscine hydrobromide																
Odachi 2017[43]	✓	–	–	–	–	–	–	–	–	✓	–	–	–	–	–	–
Ipratropium bromide																
Thomsen 2007 (NCT00296946)[46]	✓	✓	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Sockalingam 2009[57]	–	–	–	–	–	✓	–	–	–	–	✓	–	–	–	–	–
Tropicamide																
Perez-Lloret 2011 (NCT00761137)[44, 45, 59]	–	–	–	–	–	–	–	–	–	✓	✓	✓	✓	–	–	–
Amisulpride																
Kreinin 2006[52]	–	–	–	–	–	–	–	–	–	✓	✓	✓	–	–	–	–
Metoclopramide																

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Primary Outcome	Unstimulated salivary flow (g/min); saliva weight/volume (g)				Global Impression of Change (-3 to +3)					Change in drooling severity[a]						
Kreinin 2016[53]	–	–	–	–	–	–	–	–	–	✓	✓	✓	–	–	–	–
Pirenzepine																
Bai 2001[49]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	✓	✓
Atropine																
De Simone 2006[51]	–	–	–	–	–	–	–	–	–	✓	–	–	–	–	–	–
Glycopyrrolate and Biperiden																
Liang 2010[54]	–	–	–	–	–	–	–	–	–	✓	✓	✓	✓	–	–	–

Where a tick (✓) denotes that the outcome is reported at the given timepoint, and a dash (–) denotes the outcome was not reported.
[a]DSFS employed in SIAXI; various other measures employed in the different studies including NHRS, DRS and VAS scores. [b]Sialorrhoea scoring scale used to measure improvement in sialorrhoea scoring scale and responder rate was defined as an improvement by at least 30%. [c]Unable to obtain full text of Colen-De (2015)[50].
Abbreviations: g: grams; g/min: grams per minute.

Several of the trials (SIAXI, Narayanaswami 2016, Odachi 2017 and Thomsen 2007) used an objective measure of efficacy, in the form of unstimulated salivary flow (uSFR in g/min) or saliva volume/weight (g).[35-39, 41-43, 46] However, differences between methods of measurement in each trial were noted:

- SIAXI measured saliva by inserting oral swabs (2 mL capacity) into patients' mouths for 5 minutes, and then repeated after 30 minutes and an average taken of the two measurements[35-39]
- Narayanaswami 2016 measured saliva that was expelled into a pre-weighed cup for 5 minutes, averaged over two measurements (time between measurements not reported)[41, 42]
- Odachi 2017 assessed saliva weight using the weight of oral cotton roll placed into patients' mouths for 5 minutes, though the number of rolls used was not specified. Measurements also considered the volume of daily oral suction, which was not clearly defined. It is also unclear whether measurements were repeated[43]
- Thomsen 2007 also used cotton rolls up to the maximum tolerated by the patient (average 3-5) for 5 minutes.[46] It is unclear whether the measurement was repeated; measurements were also conducted whilst patients (all with Parkinson's Disease) were on levodopa medication, which may have had a confounding effect on saliva production[17]

All of the trials that were captured also used subjective rating scales to measure saliva output, including the DSFS (SIAXI, Narayanaswami 2016),[35-39, 41, 42] Thomas-Stonell and Greenberg scale (Mato 2010),[31] use of a VAS (Brodtkorb 1988, Perez-Lloret 2011),[44, 48] drooling domain of the ALSFRS-R Scale (Odachi 2017),[43] salivation domain of the UPDRS (Thomsen 2007),[46] and a self-defined sialorrhoea score (Arbouw 2010).[47] It is unclear whether there is any clinically-established precedent to combine or convert between these scales, given that different scales pose differing criteria and may be disease-specific. It is important to consider that the disease-

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specific scales captured are designed to assess the severity and/or frequency of drooling in the context of the underlying condition, whereas generic scales are not necessarily adjusted for nuanced differences between patients with sialorrhoea secondary to different indications. Narayanaswami 2016 discussed the lack of concordance between results and validated outcome measures, which was informed by a separate pragmatic review and meta-analysis that the authors conducted on botulinum toxins.[41, 42] The authors cited similar difficulties with study heterogeneity in their meta-analysis.

Safety outcomes

A summary of safety outcomes is given in Table 31. In general, the reporting of safety data was inconsistent across the captured trials. The only domain that was consistently reported was all-cause discontinuation, which was mentioned at least briefly in each trial captured. The reporting of overall AEs and serious AEs was poor overall, which were only recorded in three and two trials, respectively.

Table 32 summarises adverse events of specific interest to the interventions used to treat sialorrhoea. Dry mouth was reported across half of the trials captured, but other specific adverse events were reported sporadically. Compared to SIAXI, the trials captured had small sample sizes which affects the likelihood of observing adverse events within the studies and thus the observed safety profiles. The majority of studies were also short, thus limiting the potential occurrence of treatment-related adverse events among patients that may have emerged over a longer treatment period, as well as limiting the total number of patient-years exposure to each intervention. Considering this and the length of the SIAXI trial versus the other studies captured (with the exception of Narayanaswami 2016), it is not appropriate to perform an ITC of the safety outcomes across these interventions.

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Table 31: Summary of safety outcomes reported across captured trials

Study	Timepoints	Overall AEs	Specific AEs	Serious AEs	All-cause discontinuation	AEs leading to discontinuation
Xeomin						
SIAXI (NCT02091739)[35-39]	Week 16	✓	✓	✓	✓	✓
Narayanaswami 2016 (NCT01653132)[41, 42]	Month 8	–	✓	–	✓	–
Glycopyrrolate (glycopyrronium bromide)						
Arbouw 2010[47]	Week 4	–	✓	✓	✓[d]	–
Colen-De 2015[50]	–	–	–	–	–	–
Man 2017[55]	NR	✓	–	–	–	–
Hyoscine hydrobromide						
Brodtkorb 1988[48]	NR	✓[a]	✓[a]	–	✓	–
Mato 2010[31]	Week 5[b]	–	✓	–[c]	✓	✓
Takeuchi 2017[58]	NR	–	–	–	–	–
Odachi 2017[43, 60]	Week 4[b]	–	✓	–	✓	✓
Ipratropium bromide						
Thomsen 2007 (NCT00296946)[46]	Week 7[b]	–	✓	–	✓	–
Sockalingam 2009[57]	Week 2	✓[e]	–	–	–	–
Tropicamide						
Perez-Lloret 2011[44, 45, 59]	Week 4	✓	–	–	✓	–

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Amisulphide						
Kreinin 2006[52]	NR	–	–	–	–	–
Metoclopramide						
Kreinin 2016[53]	NR	–	–	–	–	–
Pirenzepine						
Bai 2001[49]	NR	–	–	–	–	–
Atropine						
De Simone 2006[51]	NR	–	✓	–	–	–
Glycopyrrolate and Biperiden						
Liang 2010[54]	Weeks 1-4	✓	–	–	–	–

Where a tick (✓) denotes that the outcome is reported at the given timepoint, and a dash (–) denotes the outcome was not reported
[a]Study records AEs as "comments", which may refer to each time an adverse event was recorded, rather than patients affected. [b]Timepoint not stated but based on the assumption that all adverse events were reported at the end of the trial. [c]AEs recorded as "moderate" only; no definition provided. [d]One patient excluded due to protocol violation. [e]Side effects reported as per the CGI-Side Effect scale.
Unable to obtain full text of Colen-De (2015)[50]
Abbreviations: AE: adverse event; NR: not reported.

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Table 32: Summary of adverse events of specific interest across the captured trials

Study	Timepoint	Threshold	Dry mouth	Dry Nasal passages	Dysphagia	Aspirational Pneumonia/ Pneumonia	URTI	Grade 3/4 AEs	Treatment related AEs	TRAEs leading to discontinuation
Xeomin										
SIAXI (NCT02091739)[35-39]	16 Weeks 64 Weeks	5%	✓	–	✓	✓	✓	–	✓	✓
Narayanaswami 2016 (NCT01653132)[41, 42]	8 Months	0%	–	–	–	–	–	–	✓	–
Glycopyrrolate (glycopyrronium bromide)										
Arbouw 2010[47]	4 Weeks	NR	✓	–	–	–	–	–	✓	–
Colen-De 2015[50]	–	–	–	–	–	–	–	–	–	–
Man 2017[55]	NR	NR	–	–	–	–	–	–	–	–
Hyoscine hydrobromide										
Brodtkorb 1988[48]	NR	NR	✓	–	–	–	–	–	–	–
Mato 2010[31]	5 Weeks	NR	–	–	–	–	–	–	✓	✓
Takeuchi 2017[58]	NR	–	–	–	–	–				

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Study	Timepoint	Threshold	Dry mouth	Dry Nasal passages	Dysphagia	Aspirational Pneumonia/ Pneumonia	URTI	Grade 3/4 AEs	Treatment related AEs	TRAEs leading to discontinuation
Odachi 2017[43, 60]	4 Weeks	NR	✓	–	–	✓	–	–	–	–
Ipratropium bromide										
Thomsen 2007 (NCT00296946)[46]	7 Weeks	NR	–	✓	–	–	–	–	✓	–
Sockalingam 2009[57]	NR	NR	–	–	–	–	–	–	–	–
Tropicamide										
Perez-Lloret 2011(NCT00761137)[44, 45]	4 Weeks	5%	–	–	–	–	–	–	–	–
Amisulphide										
Kreinin 2006[52]	NR	NR	–	–	–	–	–	–	–	–
Metoclopramide										
Kreinin 2016[53]	NR	NR	–	–	–	–	–	–	–	–
Pirenzepine										
Bai 2001[49]	NR	NR	–	–	–	–	–	–	–	–

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Study	Timepoint	Threshold	Dry mouth	Dry Nasal passages	Dysphagia	Aspirational Pneumonia/ Pneumonia	URTI	Grade 3/4 AEs	Treatment related AEs	TRAEs leading to discontinuation
Atropine										
De Simone 2006[51]	NR	NR	✓	–	–	–	–	–	–	–
Glycopyrrolate and Biperiden										
Liang 2010[54]	NR	NR	–	–	–	–	–	–	–	–

Where a tick (✓) denotes that the outcome is reported at the given timepoint, and a dash (–) denotes the outcome was not reported.
Unable to obtain full text of Colen-De (2015)[50]
Abbreviations: AE: adverse event; NR: not reported; TRAE: treatment related adverse event; URTI: upper respiratory tract infection.
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B.2.9.4 Quality assessment and risk of bias

An overview of the quality assessments of each trial is presented in Appendix D. Many of the questions were answered as either unclear or not reported. Considering these answers as negative responses (i.e. risk of bias present) to the respective questions means that none of the trials adequately reported the concealment of treatment allocation, and only two studies employed an intention-to-treat (ITT) analysis. Considered overall, Brodtkorb 1988 can be summarised as being the most susceptible to bias, though the relative age of this publication versus the other studies captured means that changes in reporting and overall transparency over time should be considered. Mato 2010, Thomsen 2007 and Odachi 2017 are also likely to be at higher risk of bias as only three out of eight responses were recorded as positive (i.e. low risk of bias). All three trials were susceptible to bias through lack of reporting of allocation concealment methods, failing to report whether there were any between-arm differences, and whether they used ITT analyses. Mato 2010 also reported an imbalance in dropouts between arms; this information could not be clearly discerned from Thomsen 2007 or Odachi 2017. This may mean that the results of the captured studies are confounded by hidden biases, introducing further heterogeneity between the studies.

B.2.9.5 Uncertainties in the indirect and mixed treatment comparisons

Due to the limitations discussed above, it was not deemed feasible to conduct an indirect or mixed treatment comparison for Xeomin versus glycopyrronium bromide (or any other anticholinergic therapy) in terms of efficacy or safety.

This is a similar finding to that stated in NG62 for cerebral palsy in under 25s, which was that *"Unfortunately, there is insufficient evidence to accurately estimate the cost-effectiveness of interventions for drooling, particularly in relation to efficacy. The comparative evidence on interventions to optimise saliva control were generally of poor quality and side-effects profiles did not reflect those observed in UK clinical practice according to the Committee. Where there was more than 1 study reporting the effectiveness of the intervention it was not thought appropriate to synthesise these data due to the various scales used to measure the severity and/or frequency of drooling, and/or the time after intervention when the outcome was measured."* Furthermore, an in-depth systematic review of the medical literature investigating the efficacy of anticholinergic drugs to treat drooling in children with multiple disabilities found that because of the methodological drawbacks within the studies and the small number of reports, no general conclusion could be reached and a meta-analysis could not be performed.[61] The authors concluded that there was some evidence that at least three anticholinergic drugs (benzatropine, glycopyrronium and trihexyphenidyl hydrochloride) are effective in the treatment of drooling in this patient group. However, it could not be concluded that one anticholinergic drug was preferable to others.[61]

Feedback from UK clinical experts experienced in the clinical management of sialorrhoea in adults was that the efficacy of glycopyrronium bromide is by far inferior to that of Xeomin, and that there is no long-term data assessing the safety and/or efficacy of glycopyrronium bromide.[1] Furthermore, in terms of safety, feedback from UK clinical experts strongly suggested that treatment with glycopyrronium bromide is associated with a higher rate of AEs than Xeomin, particularly dry mouth, agitation/nervousness, constipation and nausea.[1]

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B.2.10 Adverse reactions

The safety and tolerability of Xeomin was assessed in the SIAXI trial by monitoring and recording potential adverse events (AEs) according to MedDRA [version 18.1]).

Patients were monitored for AEs at every study visit from the time of informed consent until the patient's final study visit. Data on the occurrence of treatment emergent adverse events (TEAEs; those that arose, regardless of the study drug), adverse events of special interest (AESIs; those that possibly indicated toxin spread) and serious adverse events (SAEs; those that resulted in death, were life threatening, or met a number of other criteria) was collected through patient's spontaneous description, investigator inquiry, or discovery during clinical examinations performed at the visit. Patients were also actively questioned for occurrence of AESIs at every visit after the first injection. As described in Table 6 in Section B.2.4, the safety populations for the MP and EP included all patients who received study medication during the MP or EP, respectively.

B.2.10.1 Main Period

Extent of exposure – MP

[redacted] 33.[40]

Table 33: Classified injection cycle length – MP (SES-MP)

Classified injection cycle length, n (%)	Total Xeomin (N=148)	Xeomin 100 U (N=74)	Xeomin 75 U (N=74)	Placebo (N=36)
<14 weeks	[redacted]	[redacted]	[redacted]	[redacted]
14-18 weeks	[redacted]	[redacted]	[redacted]	[redacted]
>18 weeks	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MP: main period; SES-MP: safety evaluation set (main period); U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Adverse events – MP

Summary of adverse events – MP

Treatment-emergent adverse events (TEAEs) in the MP were defined as AEs with onset or worsening at or after the first injection of Xeomin or placebo up to and before the first injection of the EP or, in the case of discontinuation before the EP, up to and including 16 weeks after the first injection or the date of the last study visit, whichever was later. Every worsening of a TEAE was evaluated as a further TEAE. TEAEs deemed to be treatment-related were analysed separately and referred to as treatment-related TEAEs.

An overview of all patients experiencing TEAEs and treatment-related TEAEs in the MP is provided in Table 34. Less than half of all patients experienced any TEAEs, and the frequency of

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TEAEs was very similar across all three treatment groups (45.9%, 43.2%, and 41.7%, in the Xeomin 100 U, Xeomin 75 U, and placebo groups, respectively), highlighting the safety and tolerability of Xeomin.

The frequency of treatment-related TEAEs was also similar between the treatment groups (8.1%, 9.5%, and 8.3%in the Xeomin 100 U, Xeomin 75 U, and placebo groups, respectively). Overall, a very small proportion (6.8% of patients each in the Xeomin 100 U and Xeomin 75 U groups, and none of the patients in the placebo group) had treatment-emergent adverse events of special interest (TEAESIs).

A slightly higher proportion of patients in the Xeomin 100 U group (12.2%) had treatment-emergent serious adverse events (TESAEs) than in the other two groups (placebo: 8.3%, Xeomin 75 U: 8.1%), but no TESAEs in any group were considered to be related to treatment. TEAEs leading to study discontinuation occurred in only two patients, one in each Xeomin dose group, respectively, but neither were deemed to be treatment-related. No TEAEs were fatal.

Table 34: Overall summary of TEAEs – MP (SES-MP)

Number of patients with at least one AE, n (%)	Total Xeomin (N=148)	Xeomin 100 U (N=74)	Xeomin 75 U (N=74)	Placebo (N=36)
Any TEAE	66 (44.6)	34 (45.9)	32 (43.2)	15 (41.7)
Treatment-related TEAEs	13 (8.8)	6 (8.1)	7 (9.5)	3 (8.3)
Any TEAESI	10 (6.8)	5 (6.8)	5 (6.8)	0 (0.0)
Treatment-related TEAESIs	4 (2.7)	1 (1.4)	3 (4.1)	0 (0.0)
Any TESAE	15 (10.1)	9 (12.2)	6 (8.1)	3 (8.3)
Treatment-related TESAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any TEAE leading to discontinuation	2 (1.4)	1 (1.4)	1 (1.4)	0 (0.0)
Treatment-related TEAEs leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any fatal TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any treatment-related fatal TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

TEAEs were defined as AEs with onset or worsening at or after the first injection of Xeomin or placebo up to and before the first injection of EP or, in case of discontinuation before the EP, up to and including 16 weeks after the first injection or the date of last study visit, whichever was later. AESIs as defined in Table 36.
Abbreviations: AE: adverse event; MP: main period; SES-MP: safety evaluation set (main period); TEAE: treatment emergent adverse event; TEAESI: treatment emergent adverse event of special interest; TESAE: treatment emergent serious adverse event; U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Treatment-emergent adverse events (TEAEs) – MP

TEAEs were defined as AEs with onset or worsening at or after the first injection of Xeomin or placebo up to and before the first injection of the EP or, in the case of discontinuation before the EP, up to and including 16 weeks after the first injection or the date of the last study visit, whichever was later.

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A summary of the TEAEs reported by patients in the MP is provided in Table 35. In the Xeomin 100 U group, the most frequently reported TEAEs were tooth extraction (4 patients), dry mouth, diarrhoea, and hypertension (three patients each),[9]

[redacted]

Table 35: Summary of TEAEs in ≥3% patients in any treatment group – MP (SES-MP)

Number of patients with at least one AE, n (%)	Total Xeomin (N=148)	Xeomin 100 U (N=74)	Xeomin 75 U (N=74)	Placebo (N=36)
Any TEAE	66 (44.6)	34 (45.9)	32 (43.2)	15 (41.7)
Fall	[redacted]	2 (2.7)	[redacted]	0 (0.0)
Dry mouth	[redacted]	3 (4.1)	[redacted]	0 (0.0)
Hypertension	[redacted]	3 (4.1)	[redacted]	1 (2.8)
Contusion	[redacted]	0 (0.0)	[redacted]	0 (0.0)
Tooth extraction	[redacted]	4 (5.4)	[redacted]	0 (0.0)
Diarrhoea	[redacted]	3 (4.1)	[redacted]	1 (2.8)
Dysphagia	[redacted]	0 (0.0)	[redacted]	0 (0.0)
Urinary tract infection	[redacted]	0 (0.0)	[redacted]	0 (0.0)

TEAEs were defined as AEs with onset or worsening at or after the first injection of Xeomin or placebo up to and before the first injection of EP or, in case of discontinuation before the EP, up to and including 16 weeks after the first injection or the date of last study visit, whichever was later.
Abbreviations: MP: main period; SES-MP: safety evaluation set (main period); TEAE: treatment emergent adverse event; U: units.
Source: FDA Prescribing Information: Xeomin (Incobotulinum toxin A),[9] SIAXI Interim Clinical Study Report (16th May 2017).[40]

Treatment-emergent serious adverse events (TESAEs) – MP

TESAEs were defined as serious AEs with onset or worsening at or after the first injection of EP up to and including 16 weeks after last injection of the EP or the date of last study visit, whichever was later. A serious AE was defined as any untoward medical occurrence that at any dose resulted in death, was life threatening, required in-patient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, and/or consisted of any other medically important condition.[40]

[redacted]

Treatment emergent adverse events leading to discontinuation – MP

In the MP, two patients discontinued treatment due to TEAEs, one in the Xeomin 100 U group due to gastrointestinal obstruction, and one in the Xeomin 75 U group due to pneumonia. Both

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events were not related to the study treatment. The events were reported as resolved with sequelae at the end of the study.[40]

Treatment-emergent adverse events of special interest (TEAESIs) – MP

Adverse events that possibly indicated toxin spread were defined as AESIs. For this study, AEs listed in Table 36 were defined as AESIs. Additionally, AEs describing "Dry mouth" considered to be severe, serious or irreversible were reported as AESIs.[40]

Table 36: Adverse events of special interest in the SIAXI trial

Accommodation disorder	Eyelid ptosis	Peripheral nerve palsy
Areflexia	VIIth nerve paralysis	Peripheral paralysis
Aspiration	Facial paresis	Pelvic floor muscle weakness
Botulism	Hemiparesis	Pneumonia aspiration
Bradycardia	Hypoglossal nerve paresis	Pupillary reflex impaired
Bulbar palsy	Hyporeflexia	Quadriparesis
Constipation	Hypotonia	Respiratory arrest
Cranial nerve palsies, multiple	IIIrd nerve paresis	Respiratory depression
Cranial nerve paralysis	Ileus paralytic	Respiratory failure
Diaphragmatic paralysis	IVth nerve paresis	Speech disorder
Diplopia	Monoparesis	Trigeminal nerve paresis
Dysarthria	Muscular weakness	Urinary retention
Dysphagia	Paralysis	Vision blurred
Dysphonia	Paralysis flaccid	Vocal cord paralysis
Dyspnoea	Paraparesis	Vocal cord paresis
Extraocular muscle paresis	Paresis	
Eyelid function disorder	Paresis cranial nerve	

An overview of all patients experiencing TEAESIs in the MP is provided in Table 37. During the MP, TEAESIs were reported for five patients each (6.8%) in the Xeomin 100 U group and the Xeomin 75 U group. None of the patients in the placebo group reported TEAESIs. The most frequently reported TEAESIs were dry mouth and dysphonia in two patients each (2.7%) in the Xeomin 100 U group and dysphagia in three patients (4.1%) in the Xeomin 75 U group. All other TEAESIs were experienced by only one patient. None of the TEAESIs was serious. Two of the events of dysphagia, one of the events of dry mouth and the events of speech disorder and eyelid ptosis were deemed to be related to the study treatment.[40]

Table 37: Summary of TEAESIs – MP (SES-MP)

Number of patients with at least one AE, n (%)	Total Xeomin (N=148)	Xeomin 100 U (N=74)	Xeomin 75 U (N=74)	Placebo (N=36)
Any TEAESI	10 (6.8)	5 (6.8)	5 (6.8)	0 (0.0)
Dysphagia	3 (2.0)	0 (0.0)	3 (4.1)	0 (0.0)
Dry mouth	2 (1.4)	2 (2.7)	0 (0.0)	0 (0.0)
Dysarthria	1 (0.7)	1 (1.4)	0 (0.0)	0 (0.0)
Speech disorder	1 (0.7)	0 (0.0)	1 (1.4)	0 (0.0)
Dysphonia	2 (1.4)	2 (2.7)	0 (0.0)	0 (0.0)

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Bradycardia	1 (0.7)	0 (0.0)	1 (1.4)	0 (0.0)
Eyelid ptosis	1 (0.7)	0 (0.0)	1 (1.4)	0 (0.0)

TEAESIs as defined in Table 36. TEAEs were defined as AEs with onset or worsening at or after the first injection of Xeomin or placebo up to and before the first injection of the EP or, in case of discontinuation before the EP, up to and including 16 weeks after the first injection or the date of last study visit, whichever was later.
Abbreviations: AE: adverse event; MP: main period; SES-MP: safety evaluation set (main period); TEASI: treatment emergent adverse event of special interest; U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Deaths – MP

No patients died during the MP.[40]

Modified Radboud Oral Motor Inventory for Parkinson's Disease (mROMP) – MP

Part II of the mROMP (swallowing symptoms) was administered as a safety assessment. Parts I and III were administered as efficacy assessments (see Section B.2.6.1).

[redacted]

38 [redacted]

[redacted]

[redacted]

Table 38: Change in mROMP swallowing symptoms from study baseline to Weeks 4, 8, 12 and 16 – MP (SES-MP)

	Xeomin 100 U		Xeomin 75 U		Placebo	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Score ranges from 7 (best) to 35 (worst).
Abbreviations: MP: main period; mROMP: modified Radboud oral motor inventory for Parkinson's disease; SD: standard deviation; SES-MP: safety evaluation set (main period); U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

B.2.10.2 Extension Period

Extent of exposure – EP

In all three injection cycles of the EP, the vast majority of patients (>97%) received the dose of the group they were randomised to. The mean injection cycle length for both Xeomin treatment groups was approximately 16 weeks for each injection cycle in the EP. The investigators reduced the planned dose for five patients for safety reasons (permitted in Cycles 3 and 4 per the study protocol).[40]

Two patients received the wrong or no dose due to procedural reasons. Both were excluded from the analysis.[40]

Table 39: Classified injection cycle length – EP (SES-EP)

Classified injection cycle length	Xeomin 100 U n/N (%)	Xeomin 75 U n/N (%)
2nd injection cycle		
<14 weeks	[redacted]	[redacted]

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14-18 weeks	[redacted]	[redacted]
>18 weeks	[redacted]	[redacted]
3rd injection cycle		
14-18 weeks	[redacted]	[redacted]
>18 weeks	[redacted]	[redacted]
4th injection cycle		
<14 weeks	[redacted]	[redacted]
14-18 weeks	[redacted]	[redacted]
>18 weeks	[redacted]	[redacted]

Abbreviations: EP: extension period; SES-EP: safety evaluation set (extension period); U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Adverse events – EP

Summary of adverse events – EP

TEAEs in the EP were defined as AEs with onset or worsening at or after the first injection of Xeomin in the EP up to and including 16 weeks after the last injection of the EP or the last study visit, whichever was later. Every worsening of a TEAE was evaluated as a further TEAE. TEAEs deemed to be treatment-related were analysed separately and referred to as treatment-related TEAEs. A summary of TEAEs experienced by patients in the EP is provided in Table 40.

[redacted]

Table 40: Overall summary of TEAEs – EP (SES-EP)

Number of patients with at least one AE, n (%)	Total Xeomin (N=171)	Xeomin 100 U (N=89)	Xeomin 75 U (N=82)
Any TEAE	[redacted]	[redacted]	[redacted]
Any treatment-related TEAE	[redacted]	[redacted]	[redacted]
Any TEAESI	[redacted]	[redacted]	[redacted]
Any treatment-related TEAESI	[redacted]	[redacted]	[redacted]
Any TESAE	[redacted]	[redacted]	[redacted]
Any treatment-related TESAE	[redacted]	[redacted]	[redacted]
Any TEAE leading to discontinuation	[redacted]	[redacted]	[redacted]
Any treatment-related TEAE leading to discontinuation	[redacted]	[redacted]	[redacted]

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Any fatal TEAE	[redacted]	[redacted]	[redacted]
Any fatal treatment-related TEAE	[redacted]	[redacted]	[redacted]

TEAEs were defined as AEs with onset or worsening at or after the first injection of Xeomin or placebo up to and before the first injection of the EP or, in case of discontinuation before the EP, up to and including 16 weeks after the first injection or the date of last study visit, whichever was later. TAESIs as defined in Table 36.
Abbreviations: AE: adverse event; EP: extension period; SES-EP: safety evaluation set (extension period); TEAE: treatment emergent adverse event; TEAESI: treatment emergent adverse event of special interest; TESAE: treatment emergent serious adverse event; U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Treatment-emergent adverse events (TEAEs) – EP

[redacted] A summary of the most frequent TEAEs can be found in Appendix F.

Treatment-emergent serious adverse events (TESAEs) – EP

[redacted]

Adverse events leading to discontinuation – EP

[redacted]
41 [redacted]

Table 41: TEAEs leading to discontinuation – EP (SES-EP)

Number of patients with at least one AE, n (%)	Total Xeomin (N=171)	Xeomin 100 U (N=89)	Xeomin 75 U (N=82)

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Any TEAE leading to discontinuation	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]
Dental caries	[redacted]	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]	[redacted]
Salivary hypersecretion	[redacted]	[redacted]	[redacted]
Altered state of consciousness	[redacted]	[redacted]	[redacted]
Dementia	[redacted]	[redacted]	[redacted]
Psychomotor hyperactivity	[redacted]	[redacted]	[redacted]
Coagulopathy	[redacted]	[redacted]	[redacted]
Cardio respiratory arrest	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]
Mobility decreased	[redacted]	[redacted]	[redacted]
Delusion	[redacted]	[redacted]	[redacted]
Dopamine dysregulation syndrome	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]

TEAEs were defined as AEs with onset or worsening at or after the first injection of EP up to and including 16 weeks after the last injection of the EP or the last study visit, whichever was later.
Abbreviations: AE: adverse event; EP: extension period; SES-EP: safety evaluation set (extension period); TEAE: treatment emergent adverse event; U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

Treatment-emergent adverse events of special interest (TEAESIs) – EP

A summary of all patients experiencing TEAESIs in the EP is shown in Table 42.

[redacted]

Table 42: Number (%) of patients with TEAESIs – EP (SES-EP)

Number of patients with at least one AE, n (%)	Total Xeomin (N=171)	Xeomin 100 U (N=89)	Xeomin 75 U (N=82)
Any TEAESI	[redacted]	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Speech disorder	[redacted]	[redacted]	[redacted]
Dysarthria	[redacted]	[redacted]	[redacted]
Hypotonia	[redacted]	[redacted]	[redacted]
Pneumonia aspiration	[redacted]	[redacted]	[redacted]

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Dyspnoea	[redacted]	[redacted]	[redacted]
Urinary retention	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]	[redacted]

TEAESIs are defined in Table 36. TEAEs were defined as AEs with onset or worsening at or after the first injection of the EP up to and including 16 weeks after the last injection of the EP or the date of the last study visit, whichever was later.
Abbreviations: AE: adverse event; EP: extension period; SES-EP: safety evaluation set (extension period); TEAESI: treatment emergent adverse event of special interest; U: units.
Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

[redacted]

[redacted]

[redacted]

Deaths – EP

[redacted]

Modified Radboud Oral Motor Inventory for Parkinson's Disease (mROMP) – EP

[redacted]

Table 43: Change in mROMP swallowing symptoms from study baseline – EP to all assessment visits in the EP (SES-EP)

	Xeomin 100 U		Xeomin 75 U	
	N	Mean (SD)	N	Mean (SD)
Change from study baseline to:				
Cycle 2 Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4 Week 4	[redacted]	[redacted]	[redacted]	[redacted]

Score ranges from 7 (best) to 35 (worst).
Abbreviations: EP: extension period; mROMP: modified Radboud oral motor inventory for Parkinson's disease; SD: standard deviation; SES-EP: safety evaluation set (extension period); U: units.

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Source: SIAXI Interim Clinical Study Report (16th May 2017).[40]

B.2.10.3 Conclusions on the safety of Xeomin

Overall, the frequency of TEAEs was similar between the Xeomin treatment groups and the placebo group, hence the safety profile of Xeomin was almost identical to that of receiving no treatment. In addition, no new or unexpected safety concerns were identified compared with the long-term and established use of Xeomin in other indications.
[redacted], and the most frequent TEAEs were due to the underlying neurological disease and advanced age of the study population (worsening of Parkinson's disease, fall, contusion, and tooth extraction) or were expected effects of Xeomin for the treatment of patients with sialorrhoea (dry mouth and dysphagia). Across the whole study, [redacted]. Overall, long-term treatment of chronic sialorrhoea with 100 U or 75 U of Xeomin was safe and well tolerated.

The safety data for Xeomin from SIAXI trial should be taken in the context of the AEs experienced by patients who receive glycopyrronium bromide. As discussed in Section B.1.3.2, as cholinergic transmission is vital to the correct functioning of organs such as the bladder, glycopyrronium bromide is therefore associated with numerous unwanted effects in other organ systems, including urinary retention, constipation, increased intraocular pressure, cessation of perspiration with increased body temperature and double vision.[15, 29, 30] Feedback from UK clinical experts experienced in the treatment of sialorrhoea strongly suggested that treatment with glycopyrronium bromide is associated with a higher rate of AEs than Xeomin, particularly dry mouth, agitation/nervousness, constipation and nausea.[1] The availability, therefore, of a therapy that offers long-term efficacy for the treatment of sialorrhoea with a safety profile that is well-tolerated and similar to that of placebo, represents a step-change in the first-line management of this vastly debilitating condition.

B.2.11 Ongoing studies

No further clinical trials or analyses from the SIAXI trial are anticipated in the next 12 months.

B.2.12 Innovation

Xeomin represents the first and only neurotoxin anticipated to be licensed in this indication. As a botulinum toxin type A, Xeomin is an acetylcholine release inhibitor which penetrates cholinergic nerve terminals and degrades synaptosome associated protein (SNAP)-25 proteins, thereby blocking cholinergic transmission at the neuroglandular junction by preventing the fusion of neurosecretory vesicles containing acetylcholine with the plasma membrane, inhibiting the release of acetylcholine by the nerve terminus.[9] The rate at which the submandibular and parotid glands secrete fluid is partially controlled by cholinergic signals from the surrounding nerves, and so the injection of Xeomin into these glands reduces the rate at which saliva is produced.

As discussed in Section B.1.3.2, NICE clinical guidelines for a variety of neurological conditions suggest the use of anticholinergic therapies as first-line pharmacological management of sialorrhoea.[24-26] However, there is only limited evidence supporting these drugs as effective interventions, and there are currently no licensed anticholinergic therapies for adult patients with chronic sialorrhoea. Additionally, anticholinergic therapies are associated with numerous AEs, including urinary retention, blurred vision and confusion.[15] Patients may also experience excessively dry mouth, which can result in further impairment to QoL.[15, 29, 32] Anticholinergics are not specific to the muscarinic receptors of the salivary glands. As such, patients using these

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medications for sialorrhoea management risk unwanted effects in other organ tissues, including constipation, increased intraocular pressure, cessation of perspiration with increased body temperature and double vision.[15, 29] Furthermore, anticholinergics can affect the central nervous system, causing AEs such as confusion, disorientation, memory problems, sedation and nausea, which can often be intolerable, especially in the elderly.[15, 29, 32] Therefore, there is a clear unmet need for licensed, effective, and tolerable therapies for the treatment of adult patients with chronic sialorrhoea.

The efficacy of Xeomin has been demonstrated in the SIAXI trial, a large, multicentre, RCT, where treatment with Xeomin resulted in consistent, significant reductions in salivary flow rate (uSFR), leading to consistent, positive and clinically relevant improvements in sialorrhoea (GICS, response rate, DSFS, mROMP) (See Section B.2.6). In contrast to anticholinergics, Xeomin is administered as localised injections, which may reduce the likelihood of off-target effects. As such, like other botulinum toxins, Xeomin may be associated with an improved safety profile, with fewer AEs than anticholinergic therapies.[15] This is corroborated by evidence from the SIAXI trial, where the frequency of AEs was similar between patients receiving active Xeomin treatment and placebo (in the MP, 45.9% and 43.2% of patients experienced any TEAE in the Xeomin 100U and 75U groups, respectively, compared with 41.7% of patients in the placebo group) (See Section B.2.10.1). Furthermore, respondents from a UK survey of neurologists who reported using botulinum toxin to treat sialorrhoea in patients with motor neuron disease (14 of 21 centres) indicated that botulinum toxin had one of the best AE profiles, and feedback from UK clinical experts strongly suggested that treatment with glycopyrronium bromide is associated with a higher rate of AEs than Xeomin, particularly dry mouth, agitation/nervousness, constipation and nausea.[16] [1]

Whilst the injectable administration of Xeomin is more invasive, it has a substantially lower frequency of administration schedule compared with anticholinergic therapies. The anticipated SmPC for Xeomin for chronic sialorrhoea is that Xeomin should be administered *"no sooner than every 16 weeks"*, whereas the summary of product characteristics (SmPC) for glycopyrronium bromide for the treatment of severe drooling of saliva in children and adolescents states that treatment should be administered orally *"three times a day, one hour before or two hours after meals".*[9, 28] This represents a substantial burden to both patients and caregivers, hence the injectable administration of Xeomin is likely to contribute to improved adherence and a longer-lasting effect on the condition for patients.

Finally, the innovative nature of Xeomin has been recognised by the US Food and Drugs Administration (FDA): Xeomin is first in its class, as the only treatment approved by the FDA for treatment of sialorrhoea (July 2018). Xeomin was also granted a priority review designation, which is indicative of its potential to provide significant improvements in the safety and effectiveness of the treatment for sialorrhoea. Xeomin has also been recognised by NICE as an effective treatment for sialorrhoea, reflected in the NICE guidelines for a variety of neurological conditions, which recommend use of botulinum toxin type A, generally if treatment with anticholinergics is not effective, not tolerated or contraindicated.[24-26] Furthermore, in an economic analysis carried out as part of the NG62 guidelines (cerebral palsy in under 25s, August 2016) botulinum toxin type A injections were considered to be more effective than both glycopyrrolate bromide and hyoscine hydrobromide for the treatment of drooling.

In summary, as an innovative therapy, Xeomin has the potential to provide significant, consistent improvements in sialorrhoea, whilst minimising AEs and reducing the administrative burden on patients and caregivers, for a condition with considerable unmet need.

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B.2.13 Interpretation of clinical effectiveness and safety evidence

Principal findings from the clinical evidence base

Evidence for the efficacy and safety of Xeomin as a treatment for adult patients with chronic sialorrhoea is provided from the SIAXI trial, which is a completed, prospective, randomised, double-blind, placebo-controlled, parallel-group, multicentre, Phase III study[35, 36, 38, 39]. The trial included two treatment periods: the main period (MP), comprising one treatment cycle (16±2 weeks), and an extension period (EP), comprising a further three treatment cycles (each 16±2 weeks). Overall, 184 patients were randomised (in a 2:2:1 ratio) and treated in the MP: 74 patients in each Xeomin dose group (100 U and 75 U) and 36 patients in the placebo group.[35] A total of 173 patients completed the MP and entered the EP, where 84 and 89 patients were treated with 75 U and 100 U of Xeomin, respectively. Patients who had been treated with placebo in the MP were randomised (in a ratio of 1:1) to the two Xeomin dose groups. The key findings from the SIAXI trial suggest that Xeomin, as per the anticipated licensed dose of 100 U, may offer:

Statistically significant, consistent reductions in uSFR versus placebo

- LS-Mean change in uSFR from baseline to Week 4 was -0.13 (SE: 0.026) in the Xeomin 100 U versus -0.04 (SE: 0.033) in the placebo group (p=0.004)

Clinically relevant reductions in mean uSFR were maintained through to Week 16 (i.e. over a full treatment cycle) in the MP

- Mean uSFR continued to reduce over multiple treatment cycles in the EP

Statistically significant, consistent improvements in functioning (GICS) versus placebo

- LS-Mean GICS score at Week 4 was 1.25 (SE: 0.144) (i.e. an impression of change between minimally improved and much improved) compared with 0.67 (SE: 0.186) in the placebo group (i.e. an impression of change between no change in function and minimally improved), (p=0.002)

Clinically relevant improvements in GICS were maintained through to Week 16 (i.e. over a full treatment cycle) in the MP

- Positive entries (i.e. improvements in symptoms) were reported at all visits in the EP, and a slight increase was observed over the course of the study

Statistically significantly improved response rates (based on GICS) versus placebo

- [redacted]

Statistically significant, consistent improvements in drooling severity and frequency (DSFS) versus placebo

- A significantly greater change from baseline in DSFS sum score was observed in the Xeomin 100 U group compared with placebo at Weeks 4, 8 and 12 (p<0.05)

- [redacted]

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- The DSFS sum score improved from study baseline to each Week 4 visit of the individual injection cycles in the EP

Improvements in GICS and DSFS indicate a clinically meaningful improvement in sialorrhoea as a result of treatment with Xeomin, via reduction in uSFR. Patient satisfaction with Xeomin treatment is indicated by the high trial retention rate: 94.0% of patients completed the MP, and 87.3% of patients who continued to the EP completed the study, corresponding to an overall retention rate of 82.1%.

The safety analysis of the SIAXI trial showed that long term treatment of chronic sialorrhoea with Xeomin was safe and well tolerated. In both the MP and the overall period of the EP, the frequency of TEAEs was similar between the treatment groups and no new or unexpected safety concerns were identified. The incidence of TEAEs and TEASIs did not increase with increasing numbers of injections, and the most frequent TEAEs were due to the underlying neurological disease and advanced age of the study population (worsening of Parkinson's disease, fall, contusion, and tooth extraction) or were expected effects of Xeomin for the treatment of patients with sialorrhoea (dry mouth and dysphagia). Across the whole study, five patients died, but no deaths were related to study treatment.

Strengths and limitations of the clinical evidence base

The clinical evidence presented within this submission has been derived from an SLR of clinical trials investigating the efficacy and safety of treatment options, including Xeomin, for chronic sialorrhoea. The SIAXI trial represents the primary source of evidence for Xeomin as a treatment for adult patients with chronic sialorrhoea. A small cross-over study (NCT01653132) was also identified but was not considered in this submission due to its small sample size (N=10).

The SIAXI trial is a large, placebo-controlled RCT, and thus provides robust evidence for the safety and efficacy of Xeomin for the treatment of chronic sialorrhoea. Additionally, as discussed in Section B.2.5, the SIAXI trial can be considered of good quality. Whilst no study centres in the SIAXI trial were based in the UK, according to UK clinical experts consulted as part of the submission, the patient baseline characteristics in the SIAXI trial are considered to be generally consistent with what may be expected of patients in clinical practice in England.[1] Furthermore, the anticipated licence for Xeomin is broad, and does not specify the aetiology of sialorrhoea. The mechanism of action of Xeomin is also such that treatment effect is independent of the aetiology of the sialorrhoea. Therefore, and as implicitly recognised by the FDA (and soon to be EMA) in their provision of a broader licence for Xeomin regardless of aetiology,[2] there is no reason to suggest that the efficacy of Xeomin observed within the SIAXI trial would not translate to patients suffering from sialorrhoea due to conditions outside of those suffered by the patients within the SIAXI trial.

A key limitation of the evidence base is the lack of direct evidence identified for Xeomin versus relevant comparators to inform relative efficacy estimates, since the SIAXI trial is placebo-controlled. In total, 15 RCTs reported in 18 records were identified for anticholinergic therapies or SoC from the SLR (see Appendix D), however no studies were identified directly comparing Xeomin to any anticholinergic therapies. Following a feasibility assessment of the identified evidence, it was determined that differences in patient populations, interventions and outcome measures, as well as study design, precluded the conduct of any robust ITCs in terms of efficacy or safety.

Feedback from UK clinical experts experienced in the treatment of sialorrhoea was that the efficacy of glycopyrronium bromide is by far inferior to that of Xeomin, and there is no long-term

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data assessing the safety and/or efficacy of glycopyrronium bromide.[1] Furthermore, in terms of safety, feedback from UK clinical experts strongly suggested that treatment with glycopyrronium bromide is associated with a higher rate of AEs than Xeomin, particularly dry mouth, agitation/nervousness, constipation and nausea.[1] The availability, therefore, of a therapy that offers long-term efficacy for the treatment of sialorrhoea with a safety profile that is well-tolerated and similar to that of placebo, represents a step-change in the first-line management of this vastly debilitating condition.

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B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify any relevant economic evaluations for the treatment of adult patients with chronic sialorrhoea. The SLR was performed in August 2018 and full details of the SLR search strategy, study selection process and results are reported in Appendix G.

The SLR identified no relevant economic evaluations or studies featuring relevant health state utility or cost and resource use data associated with the treatment of adult patients with chronic sialorrhoea.

B.3.2 Economic analysis

B.3.2.1 Patient population

The patient population of the economic evaluation was adult patients with chronic sialorrhoea. This patient population is in line with the anticipated licensed indication for Xeomin (see Section B.1.2) and the decision problem addressed in this submission, as outlined in Section B.1.1. The patient population evaluated in the SIAXI trial is narrower than the anticipated licensed indication (restricted to patients with chronic troublesome sialorrhoea due to neurological conditions). However, as discussed in Section B.2.13, the mechanism of action of Xeomin is such that treatment effect is independent of the aetiology of the sialorrhoea. Therefore, and as implicitly recognised by the FDA (and soon to be EMA) in their provision of a broader licence for Xeomin, there is no reason to suggest that the efficacy of Xeomin observed within the SIAXI trial would not translate to patients suffering from sialorrhoea due to conditions outside of those suffered by the patients within the SIAXI trial. Finally, UK clinical experts agreed that outcomes from the SIAXI trial can be considered generalisable to the full eligible population in UK clinical practice.[1]

B.3.2.2 Model structure

As noted in Section B.3.1, no prior health economic evaluations for Xeomin in adult patients with chronic sialorrhoea were identified in the SLR.

Therefore, a *de novo* health economic model was constructed in Microsoft Excel to evaluate the cost-effectiveness of Xeomin versus glycopyrronium bromide and SoC in adult patients with chronic sialorrhoea. The developed model is a Markov state transition model, in which a hypothetical cohort of patients transition between health states in 16-weekly cycles over a 10-year model time horizon. This approach was considered the most appropriate modelling methodology due to its simplicity and transparency (compared with other modelling techniques such as microsimulation).

The model structure is presented in Figure 9. The DSFS sum score was used to define three “sialorrhoea severity-based” health states. This approach was taken because DSFS was deemed to be the most clinically relevant measure of sialorrhoea disease severity based on feedback from UK clinical experts in the treatment of sialorrhoea.[1] As described in Section B.2.6.1, DSFS consists of two subscales; a 5-point Likert scale for classifying ‘drooling severity’ from 1 (dry) to 5 (profuse drooling) and a 4-point Likert scale for classifying ‘drooling frequency’ from 1 (no drooling) to 4 (constant drooling). Subscale scores are summed to determine an overall score

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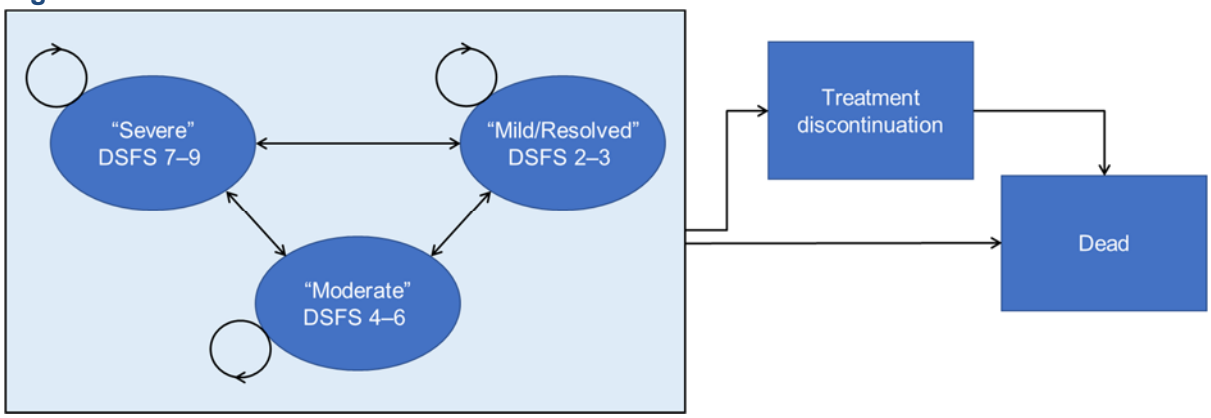
ranging from 2 to 9. The health states of the model were defined according to levels of overall sialorrhoea severity, as follows: “Severe” (DSFS 7–9), “Moderate” (DSFS 4–6) and “Mild/Resolved” (DSFS 2–3). Patients could transition between any of these health states, reflecting improvement/worsening of sialorrhoea over time. Categorising disease severity into three levels was necessary to ensure there were sufficient data to adequately capture transitions between health states, without compromising model sensitivity in capturing cost or treatment effects. It was considered that increasing health state granularity would improve model sensitivity, but increase uncertainty in the transition probabilities and health state utility estimates.

Figure 9: Model structure



Abbreviations: DSFS: Drooling Severity and Frequency Scale.

Baseline health state distributions were based on baseline DSFS scores for patients in the SIAXI trial (see Section B.3.3.1). Patients then transitioned between health states depending on changes in sialorrhoea severity experienced following treatment with the intervention or comparators. Within this model structure, the treatment benefits offered by Xeomin over the comparators were represented by a greater proportion of the modelled cohort residing in the lower severity health states over the modelled time horizon.

Patients could transition from any of these “sialorrhoea severity-based” health states to a health state representing treatment discontinuation. For patients that discontinued treatment, their sialorrhoea severity was assumed to revert to the mean severity observed at baseline. Finally, patients residing in all states could transition to the absorbing Death state. The risk of transitioning to this state was equal across all health states, as it was assumed that no excess mortality is associated with worsening sialorrhoea (see Section B.3.3.5).

Features of the economic analysis

Costs and health-related utilities were allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle. The costs considered within the model included treatment acquisition costs, associated administration costs and health state costs. Effectiveness measures included life years (LYs) and QALYs. The incremental cost-effectiveness ratio (ICER) of Xeomin versus each comparator was evaluated in terms of the incremental cost per QALY gained.

The analysis was conducted from the perspective of the UK NHS and Personal Social Services (PSS) in England over a 10-year time horizon. Feedback from UK clinical experts experienced in the treatment of sialorrhoea indicated that treatment with Xeomin may be continued for extended periods of time.[1] However, long-term efficacy data for Xeomin is lacking, so a time horizon of 10 years was considered an appropriate duration over which to fully capture the costs and benefits

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of Xeomin without introducing unnecessary extrapolation-related uncertainties. It is acknowledged that sialorrhoea is a chronic condition, and therefore scenario analyses exploring alternative longer time horizons, including a lifetime time horizon were conducted.

The cycle length employed in the Markov model was 16 weeks, reflecting the re-injection intervals in the SIAXI trial, which are consistent with recommendations in the anticipated SmPC for the administration of Xeomin.[40] The key features of the economic analysis and their justifications are presented in Table 1.

Table 44: Features of the economic analysis

	Current appraisal	
Factor	**Chosen values**	**Justification**
Model structure	Markov state transition model.	A Markov state transition model approach was chosen for its simplicity and transparency (compared with other modelling techniques like microsimulation).
Time horizon	10 years.	A time horizon of 10 years was considered an appropriate duration over which to fully capture the costs and benefits of Xeomin. Scenario analyses exploring alternative time horizons were conducted.
Source of utilities	Utility values for each severity-based health state were derived from an analysis of patient-level EQ-5D-3L scores versus DSFS scores from the SIAXI trial.	NICE reference case.
Source of drug costs	Xeomin costs were taken from the BNF online (2019) Glycopyrronium bromide costs were taken from the BNF for children (2019).	Established sources of drug costs within the NHS.
Source of other costs	NHS reference costs (2017–2018).	Established sources of costs within the NHS.
Resource use	Resource use estimates were based on feedback from UK clinical experts in the treatment of sialorrhoea.[1]	Resource use was not captured within the SIAXI trial, and no relevant resource use data were identified in the SLR.
Health effects measure	QALYs.	NICE reference case.
Discount rate for costs and QALYs	3.5% per year.	NICE reference case.
Perspective	NHS/PSS.	NICE reference case.
Half cycle correction applied?	Yes.	Half-cycle correction was applied to adjust for the bias of the assumption that transitions occur at the end or beginning of the cycle.

Abbreviations: BNF: British National Formulary; DSFS: Drooling Severity and Frequency Scale; EQ-5D-3L: EuroQoL 5-Dimensions 3-Levels; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSS: Personal and Social Services; QALY: quality-adjusted life year; SLR: systematic literature review.

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B.3.2.3 Intervention technology and comparators

The intervention of interest was Xeomin (at a dose of 100 U), administered as four injections into bilateral parotid and bilateral submandibular salivary glands per treatment cycle (16 weeks). Xeomin was modelled to be used in combination with SoC, considered to represent basic non-pharmacological sialorrhoea management.

As discussed in Section B.1.3.2, Xeomin is positioned for the first-line treatment of patients with chronic sialorrhoea, in line with the clinical evidence base provided by the pivotal SIAXI clinical trial for Xeomin reported in Section B.2 and the comparators specified in the NICE final scope for this appraisal. In this setting, according to feedback from UK clinical experts in the treatment of sialorrhoea, if patients are treated with active pharmacological therapy, the majority of patients receive treatment with systemic anticholinergic therapies; oral glycopyrronium bromide (administered as tablets or oral solution) is one of the most commonly tried anticholinergic therapies for the treatment of sialorrhoea in UK clinical practice, thus representing the most relevant comparator to Xeomin in the context of this appraisal.[1] All active therapy is also given alongside SoC hence a comparison of Xeomin plus SoC versus glycopyrronium bromide plus SoC was included in the base case analysis.

The NICE final scope also lists established clinical management without clostridium botulinum toxin A as a potential comparator for patients where anticholinergic therapies are unsuitable.[3] For these patients, established clinical management comprises basic non-pharmacological sialorrhoea management alone, i.e. SoC alone. Furthermore, feedback from UK clinical experts experienced in the clinical management of sialorrhoea indicated that a large proportion of patients go untreated in UK clinical practice, reflecting the lack of robust evidence for the long-term efficacy of anticholinergic therapies.[1] As such, SoC alone was also included as a comparator in the model. According to UK clinical experts, SoC represents basic non-pharmacological sialorrhoea management, which may include practical aids, such as bibs, as well as speech, language and occupational therapy.

Finally, feedback from UK clinical experts experienced in the clinical management of sialorrhoea also indicated that transdermal hyoscine hydrobromide and sublingual atropine sulfate may be used in some patients.[1] Comparisons of Xeomin versus these therapies have therefore also been included in scenario analyses. As for Xeomin and glycopyrronium bromide, these anticholinergic therapies were also modelled to be used in combination with SoC.

B.3.3 Clinical parameters and variables

As described in Section B.3.3.2, three sialorrhoea severity-based health states were defined based on DSFS score. Patients transitioned between the severity-based health states depending on changes in sialorrhoea severity (i.e. DSFS) experienced following treatment with the intervention or comparators, until they transitioned to either the treatment discontinuation or absorbing death states.

All clinical data and utility inputs were derived from the SIAXI trial. Data for patients in the Xeomin 100 U arm from the Main Period and Extension Period of the SIAXI trial were employed to represent the effectiveness of Xeomin plus SoC. The placebo data from the Main Period of the SIAXI trial were employed to represent the effectiveness of SoC alone in the model.

As discussed in Section B.2.9, due to the limitations of the evidence base, an indirect treatment comparison versus glycopyrronium bromide was not possible. Feedback from UK clinical experts strongly suggested that glycopyrronium bromide is far inferior to Xeomin in reducing sialorrhoea

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severity.[1] Furthermore, in an analysis conducted by NICE for the clinical guideline of cerebral palsy in under 25s, glycopyrronium bromide was considered to be less effective than botulinum toxin type A, and was associated with a mean improvement in drooling score of 3, compared with botulinum toxin type A which was assigned a mean improvement in drooling score of 4.[25]

As such, in the absence of an alternative approach, data for patients in the Xeomin 100 U arm of the SIAXI trial were employed to represent the effectiveness of glycopyrronium bromide plus SoC in the model, but reduced by 25%. This was implemented in the model by reducing the transition probabilities for patients moving to improved health states by 25%; these patients instead remained in the same health state (for those improving by one health state) or improved by only one health state (for those improving by two health states). For example, for patients in the severe health state, 25% of those transitioning to the mild/resolved health state instead transitioned to the moderate health state, and 25% of those transitioning to the moderate health state instead remained in the severe health state. Transition probabilities for patients moving to worse health states or remaining in the same health state were kept unchanged.

Given the uncertainty associated with this approach, a scenario analysis was also conducted within which it was assumed that the efficacy of glycopyrronium bromide was equivalent to that of Xeomin. This assumption of equal efficacy is considered to be highly conservative, likely resulting in an overestimate of the ICER for Xeomin versus glycopyrronium bromide.

B.3.3.1 Baseline characteristics

The baseline characteristics for the modelled cohort are provided in Table 45 alongside their appropriateness in reflecting the patient population considered in the decision problem. Mean age and the percentage of males were used alongside UK life tables to calculate the natural mortality of the general population (see modelling of mortality in Section B.3.3.5).

These inputs were based on the baseline characteristics of patients in the SIAXI trial, which were considered generalisable to the eligible population in UK clinical practice by UK clinical experts.[1]

Table 45: Patient characteristics in the model

Model parameter	Value	Source appropriateness for modelling UK sialorrhoea population
Mean age, years	65.2 years	Based on data reported in the SIAXI trial, validated by UK clinicians
Percentage male	70.7%	Based on data reported in the SIAXI trial, validated by UK clinicians

Abbreviations: UK: United Kingdom.
Source: Blitzer *et al*. (2017).[35]

The baseline health state distributions for the overall modelled cohort are provided in Table 46 This distribution was based on the baseline DSFS scores of patients in the SIAXI trial, and feedback from UK clinical experts considered this distribution to be representative of the eligible population in UK clinical practice, anticipating a roughly 1:1 ratio of patients with severe and moderate sialorrhoea.[1]

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Table 46: Baseline health state distribution

Health state	Severe (DSFS 7–9)	Moderate (DSFS 4–6)	Mild/Resolved (DSFS 2–3)
Proportion of patients at baseline (%)	54.55	45.45	0

Abbreviations: DSFS: Drooling Severity and Frequency Scale.
Source: Patient level data from the SIAXI trial.

B.3.3.2 Transitions between sialorrhoea severity-based health states

A post-hoc analysis of DSFS data from the SIAXI trial was performed to produce transition matrices that informed the movement of the modelled cohort between the three sialorrhoea severity-based health states at each model cycle.

Data were available for four injection cycles (64 weeks) for Xeomin (1 cycle in the MP and 3 cycles in the EP), but data were limited to one injection cycle (16 weeks) for placebo (SoC alone) (MP only). During the MP, DSFS was assessed at Week 4, 8, 12 and 16. However, during the EP, DSFS was only assessed at Week 4 of each injection cycle (i.e., 4 weeks after injection). As such, due to data availability, the Week 4 data from each injection cycle (across both the MP and the EP) were utilised to produce the transition matrix of the respective model cycle. Modelled transitions for Xeomin plus SoC therefore included: Baseline–W4 (1st cycle), W4–W20 (2nd cycle), W20–W36 (3rd cycle) and W36–W52 (4th cycle). Modelled transitions for SoC included: Baseline–W4 (1st cycle).

No patients were in the mild/resolved health state at baseline. As such, in the absence of data to inform the transition probability for the movement of patients out of this state in the first model cycle, this probability was assumed to be 0 (i.e. it was assumed that patients with a baseline DSFS score of 2–3 maintain this in the first cycle). This assumption had no influence on the results of the model, since no patients entered the model in this health state.

B.3.3.3 Long-term efficacy

As discussed in Section B.2.6.2, a trend was observed in the SIAXI trial indicating improvement in mean DSFS sum score with subsequent cycles of treatment for patients receiving Xeomin 100 U. This is reflected in the model by an increase in the proportion of patients in the Xeomin plus SoC treatment arm residing in the milder sialorrhoea severity-based health states during the assessment period (Cycles 1 to 4). It is plausible that this trend could have continued beyond the end of the trial period. However, since data to support this assumption was lacking, the distribution of the patient cohort across the sialorrhoea severity-based health states at the end of the trial assessment period was assumed to carry forwards over the time horizon on a last observation carried forward (LOCF) basis, with no further transitions occurring between severity-based health states after the 1st model cycle for patients receiving SoC alone, and the 4th model cycle for patients receiving Xeomin plus SoC or glycopyrronium bromide plus SoC.

As such, the model effectively assumed that patients' sialorrhoea severity had stabilised by the end of the 1st cycle for patients receiving SoC alone, and by the end of the 4th cycle for patients receiving Xeomin plus SoC or glycopyrronium bromide plus SoC, and any improvement in disease severity observed within the assessment period is maintained across the full post-assessment period (whilst patients remain on treatment). This assumption was considered reasonable for SoC alone; whilst a slight improvement in DSFS was observed across the MP, this improvement was not consistent, with worsening observed between Week 8 and Week 16.

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Worsening was also observed between Week 4 and Week 16 for the active treatment arms, but this is consistent with the mechanism of action of Xeomin, whereas no such explanation exists for placebo. Feedback from UK clinical experts experienced in the treatment of sialorrhoea considered the assumption of severity stabilisation to be very conservative for Xeomin plus SoC, since it does not allow for further improvement in sialorrhoea severity in the post-assessment period with continued Xeomin treatment.[1] Accordingly, it does not allow for worsening of sialorrhoea severity in the post-assessment period whilst patients remain on treatment. However, across all patients that have been treated with Xeomin in clinical trials or off-label in clinical practice, neutralising antibodies have never been observed. As such, there is no expectation of a treatment-waning effect, and UK clinical experts agreed that any efficacy associated with Xeomin treatment would be maintained in the long term.[1] All worsening of sialorrhoea severity in the post-assessment period is reflected in the model via treatment discontinuation, as discussed in Section B.3.3.4.

B.3.3.4 Discontinuation

Whilst no transitions occurred between the sialorrhoea severity-based health states in the post-assessment period, patients could still discontinue treatment in subsequent modelling cycles, prompting transition to the treatment discontinuation health state. Rates of all-cause discontinuation and the relevant sources are presented in Table 47. Feedback from UK clinical experts was that upon discontinuation, patients would revert to their baseline drooling severity (i.e. lose all treatment benefit accrued until that point). As such, within the base case analysis, the sialorrhoea severity for patients who discontinued treatment with either Xeomin plus SoC or glycopyrronium bromide plus SoC was assumed to revert to the mean sialorrhoea severity observed at baseline. This treatment discontinuation state was assumed to be associated with the same utility as the mean utility of patients at baseline.

Rates of treatment discontinuation for Xeomin plus SoC were informed by the SIAXI trial and extrapolation was performed on a LOCF basis. In the first cycle, the discontinuation rate for Xeomin plus SoC was based on the discontinuation rate reported in the MP of the SIAXI trial. From Cycle 2 onwards, data from across the EP (up to week 64) were used to estimate an average discontinuation rate; this was then applied from Cycle 2 onwards and assumed to apply to all subsequent cycles.

For SoC alone, the discontinuation rate reported in MP of the SIAXI trial for patients receiving placebo was used to inform the discontinuation rate for SoC alone in the first cycle of the model. Extrapolation was performed on a LOCF basis; from Cycle 1 onwards, the discontinuation rate was assumed to apply to all subsequent cycles. It is acknowledged that patients cannot strictly discontinue SoC in UK clinical practice; SoC represents basic non-pharmacological sialorrhoea management that is received regardless of treatment, as well as by untreated patients. However, data from the placebo arm of the SIAXI trial is used in the model to reflect the efficacy of SoC alone, and any improvements in the placebo arm over the MP of the trial are at least in part due to the placebo effect. Therefore, applying the discontinuation rate in the model ensures that this placebo effect is not maintained across the entire model time horizon. Scenario analyses were explored where no discontinuation rate was applied for SoC alone in the model to explore the uncertainty in this assumption.

As discussed in Section B.1.3.2, treatment with systematic anticholinergic therapies such as glycopyrronium bromide may be associated with numerous unwanted effects in other organ systems, which may lead to treatment discontinuation.[15, 29, 30] The trials identified for glycopyrronium bromide in the SLR were not long enough to inform the discontinuation rate

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applied to glycopyrronium bromide in the model.[47] As such, feedback from UK clinical experts experienced in the treatment of sialorrhoea was sought to inform the discontinuation rate for glycopyrronium bromide. The clinical experts indicated that approximately 50% of patients receiving glycopyrronium bromide would discontinue in the first 16 weeks of treatment.[1] As such, the discontinuation rate for glycopyrronium bromide in the first model cycle was assumed to be 50%, based on the feedback from UK clinical experts.[1] In subsequent model cycles, discontinuation rates were considered equivalent between Xeomin and glycopyrronium bromide, based on the assumption that the majority of treatment discontinuation with glycopyrronium bromide would occur due to AEs, and would occur within the first 16 weeks. Given the potential uncertainty in the discontinuation rates for both treatments, alternative discontinuation rates were explored extensively in scenario analyses (see Section B.3.8.3).

Finally, according to feedback from UK clinical experts experienced in the clinical management of sialorrhoea, for patients who do not discontinue, there would be no limit on the duration of treatment with Xeomin plus SoC or glycopyrronium bromide plus SoC. As such, stopping rules were not explored.[1]

Table 47: Treatment discontinuation

	Discontinuation rate (%)	Source
Xeomin plus SoC		
1st cycle	2.7%	SIAXI trial (Xeomin 100 U, all-cause discontinuation)[35]
+2 cycles	[redacted]%	SIAXI trial (Xeomin 100 U, all-cause discontinuation, excluding deaths)[40]
Glycopyrronium bromide plus SoC		
1st cycle	50.0%	Clinician estimate
+2 cycles	[redacted]%	SIAXI trial (Xeomin 100U, all-cause discontinuation, excluding deaths)[40]
SoC alone		
1st cycle	11.1%	SIAXI trial (placebo, all-cause discontinuation)[35]
+2 cycles	11.1%	Assumption

Abbreviations: AE: adverse event; CSR: clinical study report; SoC: standard of care; U: units.

B.3.3.5 Mortality

The model assumed there to be no excess mortality associated with sialorrhoea, and no mortality differentiation between treatments; the risk of transitioning to the death health state was equal across all other health states. Feedback from UK clinical experts indicated that treatment with Xeomin may be associated with a reduced mortality risk compared with glycopyrronium bromide due to differences in safety profiles, but this effect would be small and difficult to detect.[1]

Feedback from UK clinical experts suggested that patients with sialorrhoea have an increased mortality risk compared with the general population, due to the underlying aetiologies.[1] However, since the excess mortality risk for the overall eligible population is unknown and difficult to determine, only general population mortality was included in the base case analysis. The rates employed were based on the ONS National Life Tables in England and Wales for the years 2015–2017 which are specific to age and sex.[62] Excess mortality due to underlying aetiology was explored in a scenario analysis (see Section B.3.8.3).

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B.3.3.6 Adverse events

In the SIAXI trial, the frequency of AEs was similar between the Xeomin treatment groups and the placebo group (see Section B.2.10.3). As such, it is plausible to assume that the safety profile of Xeomin plus SoC is equivalent to that of SoC alone. Furthermore, as discussed in Section B.2.9, following a feasibility assessment of the identified clinical evidence, it was determined that a robust ITC between Xeomin and glycopyrronium bromide, in terms of both efficacy and safety, could not be conducted. As such, it was conservatively assumed that the safety profiles of Xeomin plus SoC and glycopyrronium bromide plus SoC were equivalent. However, feedback from UK clinical experts experienced in the treatment of sialorrhoea strongly suggested that treatment with glycopyrronium bromide is associated with a higher rate of AEs, particularly dry mouth, agitation/nervousness, constipation and nausea.[1] Given the conservative assumption that the safety profiles were equivalent across interventions and comparators, AEs were not explicitly modelled in the cost-effectiveness model.

The approach of not explicitly including specific AEs is consistent with the approach taken in the NICE appraisal for botulinum toxin in chronic migraine, in which botulinum toxin was considered to be generally well tolerated.[63]

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

The EQ-5D-3L health utilities instrument was used to collect HRQoL data in the SIAXI trial, with the results presented in Section B.2.6.3. The NICE reference case stipulates that EQ-5D data, reported directly by patients/carers, is the preferred measure of HRQoL in adults, and that valuation of HRQoL should reflect the preferences of a representative sample of the UK population. In order to explore estimation of health state utility values in the economic model, EQ-5D-3L data collected in the SIAXI trial were converted to index scores (utility values) using the UK value set based on the time trade-off technique.[64]

B.3.4.2 Mapping

Given that the SIAXI trial collected EQ-5D-3L data, no mapping was necessary for the purposes of this submission.

B.3.4.3 Health-related quality-of-life studies

An SLR was performed to identify relevant utility studies in adults with chronic sialorrhoea. The SLR was performed in August 2018 and full details of the SLR search strategy and study selection process are reported in Appendix H. No studies reporting utility data for the population of interest were identified in the SLR.

B.3.4.4 Adverse reactions

As discussed in Section B.3.3.6, AEs were not included in the cost-effectiveness model since, in the absence of a robust comparison of safety between Xeomin and glycopyrronium bromide, it was conservatively assumed that safety profiles were equivalent across the intervention and comparators.

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B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Within the cost-effectiveness analysis, utility was modelled as dependent upon sialorrhoea severity in order to derive appropriate health-state utility values.

As discussed in Section B.1.3.1, sialorrhoea can have a considerable detrimental effect on patient HRQoL; it is associated with a variety of negative sequelae including perioral dermatitis, poor oral hygiene, bad breath, increased amount of intra-oral occult bacteria, eating and speaking difficulty, sleep disturbance, dehydration and fatigue, and can have a considerable psychosocial impact on patients through social embarrassment and decreased self-esteem.[12, 15, 17, 18]

Significant improvements in uSFR, GICS and DSFS were observed in the SIAXI trial, indicating a clinically meaningful improvement in sialorrhoea as a result of treatment with Xeomin. Furthermore, the retention rate was high (82.1% across the whole study), indicating a high level of patient satisfaction with Xeomin treatment. However, as discussed in Section B.2.6.3, [redacted] This lack of improvement does not match clinical expectations, given the improvement in sialorrhoea demonstrated by the other trial outcomes.

Generic HRQoL instruments such as the EQ-5D have been shown to be insensitive to changes in disease severity in a number of disorders, particularly those that are neither painful nor life-threatening, including ophthalmology and deafness, which may apply to sialorrhoea.[65] The issue of sensitivity of HRQoL instruments has also been acknowledged in the NICE Decision Support Unit (DSU) Technical Support Document (TDS) 10.[66] It is therefore plausible that generic HRQoL instruments are not able to fully capture the HRQoL benefit associated with improvements in sialorrhoea severity. Further complication arises from the fact that patients with sialorrhoea have a variety of underlying aetiologies, for example end-stage Parkinson's disease or motor neurone disease, which can themselves have a substantial impact on HRQoL. A patient may experience difficulties in mobility, self-care and undertaking usual activities due to their condition such that a substantial improvement in sialorrhoea won't be captured using the EQ-5D, but this does not mean that the patient does not value an improvement in their sialorrhoea severity. Furthermore, for younger patients whose underlying neurological conditions may not be as debilitating, improvement in their sialorrhoea will have a substantial impact on their ability to socialise, and undergo usual daily activities with dignity.

In the absence of any relevant utility data identified in the SLR, the patient-level data from the SIAXI trial were still analysed to explore whether clinically plausible health state utility values could be derived.

Estimating health state utilities based on patient-level data from the SIAXI trial

Regression models were explored to predict EQ-5D index scores (utility values) as a function of DSFS sum scores, in order to estimate mean utility values for each severity-based health state (i.e., each DSFS score range). DSFS sum scores and the corresponding EQ-5D index scores were pooled across all data collection time-points for all patients in the SIAXI trial (n=184); it was assumed that the relationship between EQ-5D and DSFS was independent of treatment received.

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Patient-level EQ-5D index scores appeared to exhibit a multimodal distribution (see Figure 10), a phenomenon that is commonly observed for index-weighted EQ-5D data.[67] Given linear regression models are not appropriate for modelling multimodal data, the use of latent class mixed models (LCMMs) was explored. LCMMs assume the modelled population is made up of several groups, or "latent classes", with potentially different relationships to the dependent variable (EQ-5D index score); class membership is modelled via multinomial regression.[68] Maximum likelihood estimation was used to fit all LCMMs using all-available data and thus it was assumed that dropout was missing at random (MAR). All models were fit in R version 3.5.1, using the package lcmm.[69]

Figure 10: Histogram of patient-level EQ-5D index scores

Patient-level EQ-5D-3L data from the SIAXI trial were converted to index scores using the UK value set based on the time trade-off technique.
Abbreviations: EQ-5D-3L: EuroQol 5-Dimensions 3-Levels.

A variety of LCMMs were explored, with statistical fit judged by the Bayesian Information Criterion (BIC), as shown in Table 48. DSFS sum score was modelled as a categorical variable and EQ-5D index score as a continuous variable. The models incorporated random effects to account for the correlation between repeated measures of patients; random intercepts and slopes were preferred over random intercepts alone. Models with different numbers of classes were explored, with/without class-specific mean trends, and using different variables to inform class membership, including underlying aetiology, age and gender. The model with three latent classes, class-specific mean trends, and no variable specified to inform class membership (i.e. only an intercept in the multinomial model) gave the best statistical fit. The inclusion of class-specific mean trends resulted in a large number of parameters being included in the favoured model. However, the lower BIC of this model reflects that the improvement in absolute fit may warrant the additional complexity, and the plausibility of differing relationships between EQ-5D index score and DSFS sum score for the different classes of patients supports the inclusion of the additional parameters.

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The BIC-favoured LCMM produced three sets of EQ-5D index score predictions (EQ-5D index scores corresponding to each DSFS sum score), one for each latent class. As such, the predictions were combined to estimate mean utility values for each health state in the economic model. A weighted average was taken across the three classes for each DSFS score, where the weighting was based on the probabilistic posterior classification of patients being in each class. The mean utility values for each health state (i.e. DSFS score range) were then calculated, as shown in Table 49.

The results of the model predicted a difference of only 0.0423 and 0.0543 between the utility of the mild/resolved versus moderate and the mild/resolved versus severe health states, respectively. As such, the resulting health state utility values were not considered to appropriately reflect the differences in HRQoL expected given the differences in disease severity. Alternative approaches were therefore considered. Whilst no relevant utility data were identified in the SLR, health state utility values for a set of drooling severity health states were reported in a cost-effectiveness analysis conducted for the NG62 guidelines for cerebral palsy in under 25s.[25] Due to a lack of evidence, the health state utility values estimated within the guidelines were hypothetical, and based on a rationalisation of the expected potential impact of drooling severity on quality of life. These utilities set a base case disutility per unit increase in drooling severity score set to a value of 0.025. This resulted in a difference in utility of 0.2 between the least and most severe drooling health states, which was considered to be clinically plausible.

Based on feedback from UK clinical experts and consideration alongside the utility framework considered appropriate in NG62, the utility values derived from the SIAXI study via the LCMM were not considered clinically plausible, which may be due to insensitivity in the generic EQ-5D instrument to changes in sialorrhoea severity. As such, the predicted utility values from the LCMM were not used within the base case analysis and were instead explored in a scenario analysis (see Section B.3.8.3).

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Table 48: LCMMs to predict EQ-5D index scores from DSFS sum scores

Model	Linear component[a]	Number of latent classes	Class membership[b]	Class specific linear component	Random effects[c]	Number of parameters	BIC	Rank
1	~ dsfs	3	~ 1	~ 1	~ 1 + week | id	16	-654.13	2
2	~ dsfs	2	~ 1	~ 1	~ 1 + week | id	14	-635.35	8
3	~ dsfs	1	N/A	N/A	~ 1 + week | id	12	-645.78	5
4	~ dsfs	3	~ 1	~ dsfs	~ 1 + week | id	30	-654.87	1
5	~ dsfs	3	~ 1	~ dsfs	~ 1 | id	28	-651.95	3
6	~ dsfs	3	~ age	~ 1	~ 1 + week | id	18	-647.82	4
7	~ dsfs	3	~ aetiology	~ 1	~ 1 + week | id	20	-638.51	7
8	~ dsfs	3	~ gender	~ 1	~ 1 + week | id	18	-644.16	6

All models were fit to 1,385 observations pooled across all 184 patients in the SIAXI trial. The dsfs term represents the DSFS sum score as a categorical variable with eight levels; the term week represents the data collection timepoint; variable id is the patient identification number.
[a] The linear component predicts the EQ-5D index scores and is common to all classes. [b] A number of terms were explored to predict class membership in the multinomial component of the model. Aetiology is a factor with three levels (Parkinson's disease or atypical Parkinsonism, brain injury and stroke). Age was modelled as a continuous variable and gender was modelled as an indicator variable. [c] Repeated measures were accounted for through including individual specific random effects.
Abbreviations: BIC: Bayesian Information Criterion.

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Table 49: Utility values based on the favoured LCMM

Health State	Mean utility value	Difference in utility versus mild/no health state
Severe (DSFS 7–9)	0.5854	0.0543
Moderate (DSFS 4–6)	0.5974	0.0423
Mild/resolved (DSFS 2–3)	0.6397	-

Abbreviations: DSFS: Drooling Severity and Frequency Scale; LCMM: latent class mixture model; SD: standard deviation.

Estimating health state utilities based on hypothetical utility values reported in NG62

Whilst the population considered in NG62 (under 25s with cerebral palsy) is different to the population considered in this appraisal, the reported utility values represent utility values that were considered reasonable to inform a NICE clinical guideline in the absence of any other data from which to generate health-state utility values. As such, it was considered appropriate to explore the use of these values within the base case analysis.

In order to derive health state utility values based on DSFS from the utility values reported in NG62, the descriptions of the DSFS and the drooling scale adopted in NG62 were matched, and a corresponding DSFS drooling frequency or severity score (see Table 50) was applied to each of the NG62 scale descriptions (see Table 51).

Table 50: Summary of the DSFS scale

DSFS		Description
Frequency	1	No drooling
	2	Occasionally drools
	3	Frequently drools
	4	Constant drooling
Severity	1	Never drools, dry
	2	Mild - drooling, only lips wet
	3	Moderate - drool reaches the lips and chin
	4	Severe - drool drips off chin and onto clothing
	5	Profuse - drooling off the body and onto objects (furniture, books)

Abbreviations: DSFS: Drooling Severity and Frequency Scale.

Table 51: Matching of DSFS score definitions to the NG62 drooling score definitions

Hypothetical utility values (NG62)					
NG62 drooling score	**Description**	**Corresponding DSFS score**			**NG62 utility values**
		Frequency	**Severity**	**Sum score**	
1	Dry: never drools; occasionally	2	1	3	0.500
2	Mild: only the lips are wet; occasionally;	2	2	4	0.475
3	Mild: only the lips are wet; frequently;	3	2	5	0.450
4	Moderate: wet on lips and chin; occasionally	2	3	5	0.425

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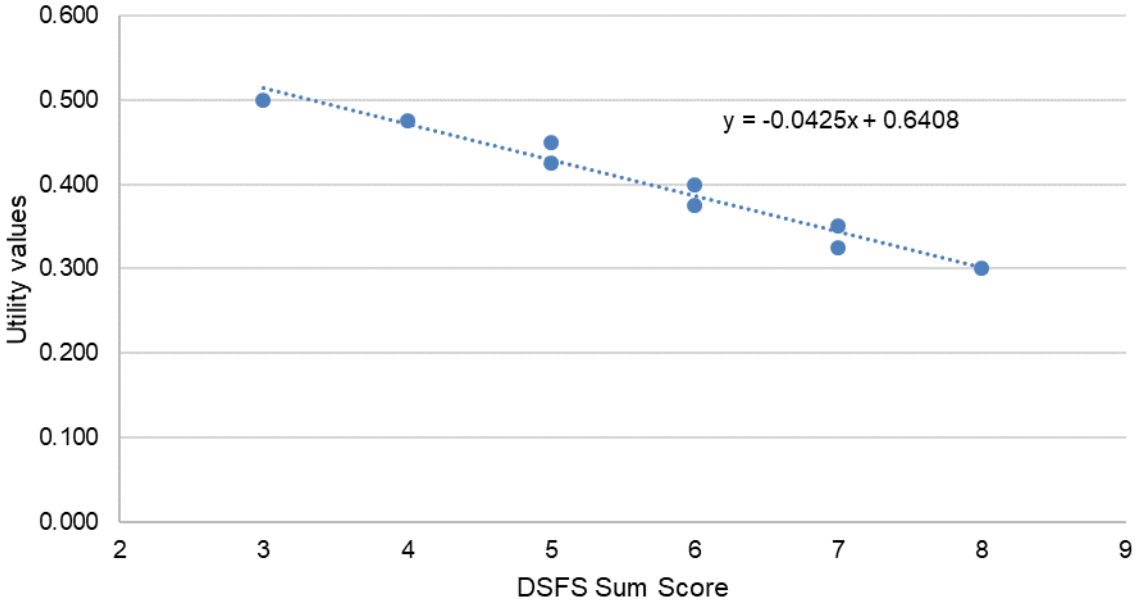
5	Moderate: wet on lips and chin; frequently	3	3	6	0.400
6	Severe: drools to the extent that clothing becomes damp; occasionally	2	4	6	0.375
7	Severe: drools to the extent that clothing becomes damp; frequently	3	4	7	0.350
8	Profuse: clothing, hands, tray and bojects become wet; occasionally	2	5	7	0.325
9	Profuse: clothing, hands, tray and bojects become wet; frequently	3	5	8	0.300

Abbreviations: DSFS: Drooling Severity and Frequency Scale.
Source: NG62.[25]

The DSFS sum score were then plotted versus the NG62 utility values, to derive utility values based on DSFS (Figure 11). The resulting utility values are presented in Table 52, and were the utility values adopted within the base case analysis.

Figure 11: Derivation of utility values based on DSFS from NG62



Abbreviations: DSFS: Drooling Severity and Frequency Scale.

Table 52: Derived utility values

DSFS	Derived utility value	Average health state utility values
2	0.5558	Mild/no sialorrhoea (DSFS 3-2): 0.5346
3	0.5133	
4	0.4708	Moderate sialorrhoea (DSFS 6-4): 0.4283
5	0.4283	
6	0.3858	
7	0.3433	Severe sialorrhoea (DSFS 9-7): 0.3008
8	0.3008	

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9	0.2583	

Abbreviations: DSFS: Drooling Severity and Frequency Scale.

As discussed in Section B.3.3.4, patients who discontinue treatment in the model were assumed to revert to the mean sialorrhoea severity observed at baseline; thus utility for these patients was calculated as a weighted average of the moderate and severe health state utility values, according to the baseline health state distribution (see B.3.3.1).

Threshold analysis

Given the uncertainty in the utility values adopted within the base case economic analysis, a threshold analysis was conducted to identify the minimum difference in utility between the mild/resolved health state and the severe health state, assuming all other assumptions in the base case hold, for Xeomin to not represent a cost-effective use of NHS resources (assuming a £30,000 per QALY threshold). The analysis was conducted in light of the results of the utility analysis conducted using EQ-5D data from the SIAXI trial that predicted a difference of only 0.0543 between the utility of the mild/resolved versus severe health state, which was not considered clinically plausible.

The results of the threshold analysis indicated that, for Xeomin to not represent a cost-effective use of NHS resources (assuming a £30,000 per QALY threshold), the difference in utility between the mild/resolved health state and the severe health state, assuming all other assumptions in the base case hold, would need to be less than 0.062. The equivalent difference in utility between the mild/resolved health state and the severe health state generated as part of NG62 was 0.2, based on a rationalisation of the expected potential impact of drooling severity on quality of life. It is acknowledged that the utility values adopted within the base case analysis are associated with unavoidable uncertainty; however, it is reasonable to assume that a difference in utility between the mild/resolved health state and the severe health state of less than 0.062 would not be reflective of the differences in utility expected with such an improvement in sialorrhoea severity in clinical practice. The difference is likely to be much greater than this, as adopted within the base case analysis.

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

An SLR was performed to identify relevant cost and healthcare resource use studies in adults with chronic sialorrhoea. The searches were performed in August 2018 and full details of the SLR search strategy and study selection process are reported in Appendix I. No studies containing relevant costs or healthcare resource use data were identified in the SLR.

Costs included in the model

The economic analysis was conducted from an NHS and PSS perspective and therefore included only costs that would be incurred by the NHS and PSS. Appropriate sources of unit costs, such as NHS reference costs (2017–2018) and the British National Formulary (BNF) online (2019) were used for cost inputs in the model.

Specifically, the following cost components were considered in the model: drug and procedure acquisition costs for the intervention and comparators, associated drug administration costs, and disease management costs (by health state).

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B.3.5.1 Intervention and comparators' costs and resource use

As discussed in Section B.3.2.3, based on feedback from UK clinical experts, both Xeomin and glycopyrronium bromide are used in conjunction with SoC in UK clinical practice. SoC is considered to represent basic non-pharmacological sialorrhoea management, which will vary patient-by-patient. Feedback from UK clinical experts suggests that this basic management varies according to sialorrhoea severity, irrespective of any pharmacological therapies received. As such, acquisition and administration costs for SoC were not considered in the model, and any variation in cost and resource use for SoC was assumed to be accounted for via differentiation in cost and resource use across the sialorrhoea severity-based health states (see Section B.3.5.2).

The unit cost and resource use associated with the acquisition and administration of Xeomin and glycopyrronium bromide are provided in Table 53.

The list price of Xeomin is £129.90 per 100 U dose, as per the BNF online (2019). This cost was applied once every 16-week cycle, according to the dosing schedule in the SIAXI trial, which is consistent with the recommendations in the anticipated SmPC for Xeomin. Administration costs per dose of Xeomin were taken from NHS reference costs (2017-2018) and were assumed to consist of an outpatient consultation and, for 56.4% of patients, an outpatient ultrasound scan. The proportion of patients modelled to receive an ultrasound to guide Xeomin administration was based on the proportion of patients who received ultrasound guidance in the SIAXI trial, and validated by feedback from UK clinical experts who suggested that ultrasound guidance was used variably in UK clinical practice.[1]

Prices for oral preparations of glycopyrronium bromide were taken from the BNF for Children online (2019), given the oral preparations of glycopyrronium bromide are unlicensed for the treatment of sialorrhoea (or any other indication) in adults. According to feedback from UK clinical experts experienced in the treatment of sialorrhoea, patients may receive glycopyrronium bromide as tablets or oral solution. As such, the cost per dose of glycopyrronium bromide was calculated as a weighted average of these two preparations, at an estimated 1:1 ratio. Feedback from UK clinical experts indicated that doses of glycopyrronium bromide may range between 0.3–1.5 mg three times a day. Therefore, glycopyrronium bromide was modelled within this range, at a dose of 1.0 mg 3 times per day, based on the dosing schedule reported in the clinical trial of glycopyrronium bromide in this indication – Arbouw *et al.* (2010) – and recommendations in the SmPC for glycopyrronium bromide for the treatment of severe drooling of saliva in children and adolescents.[28] Since glycopyrronium is administered orally, administration costs were assumed to be negligible.

Table 53: Unit costs associated with the technology in the economic model

Intervention/ comparator	Defined dosing[a]	Price per pack or vial[b]	Cost per dose[c]	Administration cost per dose[d]	Frequency per cycle	Total cost per cycle
Xeomin plus SoC	100 U per injection	100 U powder for solution for injection vial: £129.90	£129.90	£133.51	1	£286.98

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Glycopyrronium bromide plus SoC	1 mg three times daily	30 x 1 mg tablets: £180.00 150 ml x 1mg/5ml vial of oral solution: £91.00	£4.52	£0.00	336	£1,517.60

[a] The dosing schedule for Xeomin was obtained from the SIAXI trial and is consistent with the recommendations in the anticipated SmPC. The dosing schedule for glycopyrronium bromide was taken from Arbouw *et al.* (2010), and is consistent with the recommendations in the SmPC for glycopyrronium bromide for the treatment of severe drooling of saliva in children and adolescents, as well as feedback from UK clinical experts. [b] Price per vial of Xeomin was taken from the BNF online (2019). Prices for oral preparations of glycopyrronium bromide were taken from the BNF for Children online (2019). [c] According to feedback from UK clinical experts, patients may receive glycopyrronium as tablets or oral solution. As such, the cost per dose of glycopyrronium bromide was calculated as a weighted average of these two preparations, at an estimated 1:1 ratio. [d] Administration costs per dose of Xeomin were taken from the NHS reference costs (2017-2018), and were assumed to consist of an outpatient consultation (£102.96) and, for 56.4% of patients (based on the proportion of patients receiving ultrasound guidance in the SIAXI trial), an outpatient ultrasound scan (£54.12). Since glycopyrronium bromide is administered orally, administrations costs were assumed to be negligible.
Abbreviations: BNF: British National Formulary; NHS: National Health Service; SmPC: Summary of Product Characteristics; SoC: standard of care; UK: United Kingdom.

B.3.5.2 Health-state unit costs and resource use

As discussed in Section B.3.2.3, based on feedback from UK clinical experts, both Xeomin and glycopyrronium bromide are used in conjunction with SoC in UK clinical practice. SoC is considered to represent basic non-pharmacological sialorrhoea management, which may include speech, language and occupational therapy. Given basic sialorrhoea management is expected to vary according to sialorrhoea severity, the model accounted for sialorrhoea-specific resource use for the “severe” and “moderate” severity health states. No resource use data were collected in the SIAXI trial therefore the model assumed that patient in the severe severity health state required two speech pathology or occupational therapy consultations each 16-week cycle, and patients in the moderate severity health state required one speech pathology or occupational therapy consultation each 16-week cycle.

Feedback from clinical experts suggested that there may not be a large difference in resource use between the management of severe and moderate sialorrhoea, hence the requirement of one speech pathology or occupational therapy consultation each 16-week cycle in both the moderate and severe health states was explored in a scenario analysis.

Costs of speech pathology and occupational therapy consultations were derived from NHS reference costs (2017–2018).[70] Patients with mild/no sialorrhoea were assumed to require no health state sialorrhoea management.

Table 54: List of health states and associated costs in the economic model

Health state	Item	Cost[a]	Number per cycle[b]	Cost per cycle
Severe (DSFS 9-7)	Speech pathology consultation	£95.52	1	£176.83
	Occupational therapy consultation	£81.31	1	
Moderate (6-4)	Speech pathology consultation	£95.52	0.5	£88.41

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	Occupational therapy consultation	£81.31	0.5	
Mild/no (3-2)	N/A	N/A	N/A	£0.00
Baseline for discontinuers	Speech pathology consultation	£95.52	0.5	£88.41
	Occupational therapy consultation	£81.31	0.5	

[a] Costs were taken from NHS reference costs (2017–2018). [b] For severe and moderate health states, resource use was assumed to consist of either one speech pathology or occupational therapy consultation per model cycle based on clinician feedback.
Abbreviations: DSFS: Drooling Severity and Frequency Scale; N/A: not applicable.

B.3.5.3 Adverse reaction unit costs and resource use

As discussed in Section B.3.3.6, AEs were not included in the cost-effectiveness model since, in the absence of a robust comparison of safety between Xeomin and glycopyrronium bromide, it was conservatively assumed that safety profiles were equivalent across the intervention and comparators.

B.3.5.4 Miscellaneous unit costs and resource use

N/A – No miscellaneous unit costs or resource use were included in the economic model.

B.3.6 Summary of base case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

A summary of inputs for the base case analysis is presented in Table 55.

Table 55: Summary of variables applied in the economic model

Variable	Value	Reference to section in submission
Model settings		
Discount rate (costs)	3.5%	Section B.3.2.2
Discount rate (benefits)	3.5%	
Time horizon (years)	10 years	
Patient characteristics		
Starting age (years)	65.2	Section B.3.3.1
Percent male	70.7%	
Baseline health state distribution		
Severe (DSFS 7–9)	54.55%	Section B.3.3.1
Moderate (DSFS 4–6)	45.45%	
Mild/resolved (DSFS 2–3)	0.00%	
Clinical inputs		
Xeomin plus SoC discontinuation rate	• Cycle 1: 2.7% • Cycle 2+: [redacted]%	Section B.3.3.4
Glycopyrronium bromide plus SoC discontinuation rate	• Cycle 1: 50.0% • Cycle 2+: [redacted]%	
SoC alone discontinuation rate	• Cycle 1: 11.1%	

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	• Cycle 2+: 11.1%	
Mortality rate	Age- and sex-matched general population mortality	Section B.3.3.5
Utility inputs		
Utility for Severe health state (DSFS 7–9)	0.3008	Section B.3.4.5
Utility for Moderate health state (DSFS 4–6)	0.4283	
Utility for Mild/resolved health state (DSFS 2–3)	0.5346	
Utility for Baseline/Discontinued patients	0.3588	
Cost inputs		
Drug acquisition costs (per cycle)	Xeomin plus SoC: £129.90 Glycopyrronium bromide plus SoC: £1,517.60	Section B.3.5.1
Administration cost (per cycle)	Xeomin plus SoC: £133.51 Glycopyrronium bromide plus SoC: £0.00	
Severe (DSFS 7–9) health state disease management cost (per cycle)	£176.83	Section B.3.5.2
Moderate (DSFS 4–6) health state management cost (per cycle)	£88.41	
Mild/resolved (DSFS 2–3) health state management cost (per cycle)	£0.00	
Discontinuers health state management cost (per cycle)	£88.41	

Abbreviations: CI: confidence interval; DSFS: Drooling Severity and Frequency Scale; SoC: standard of care.

B.3.6.2 Assumptions

A list of the key assumptions used in the base case analysis is provided in Table 56 alongside a description of scenarios conducted to explore the impact of these assumptions on the base case cost-effectiveness results. The results of these scenario analyses are presented in Section B.3.8.3.

Table 56: List of assumptions for the base case analysis

Assumption	Description of assumption for the base case	Justification	Addressed in scenario analysis
Time horizon	The model time horizon is 10 years.	A time horizon of 10 years was considered to be an appropriate duration over which to fully capture the costs and benefits of Xeomin without introducing unnecessary extrapolation-related uncertainties.	Scenario analyses were conducted using time horizons of 2 years, 5 years, 20 years, 30 years and lifetime.
Comparator efficacy	It was assumed that the efficacy of glycopyrronium bromide plus SoC was based on that of Xeomin plus SoC but reduced by 25%.	As discussed in Section B.2.9, due to the limitations of the evidence base, an indirect treatment comparison versus glycopyrronium bromide was not possible. Feedback from UK clinical experts strongly suggested that glycopyrronium bromide is far inferior to Xeomin in reducing sialorrhoea severity.[1] Furthermore,	A scenario analysis assuming equal efficacy between Xeomin plus SoC and glycopyrronium plus SoC was conducted.

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		in an analysis conducted by NICE for the clinical guideline of cerebral palsy in under 25s, glycopyrronium bromide was considered to be less effective than botulinum toxin type A, and was associated with a mean improvement in drooling score of 3, compared with botulinum toxin type A which was assigned a mean improvement in drooling score of 4.[25] In the absence of an alternative approach, data for patients in the Xeomin 100 U arm of the SIAXI trial were employed to represent the effectiveness of glycopyrronium bromide plus SoC in the model, but reduced by 25%.	
Long-term efficacy	Extrapolation of the health state transition probabilities was conducted on a LOCF basis.	Feedback from UK clinical experts experienced in the treatment of sialorrhoea considered this assumption to be very conservative, since it does not allow for further improvement in sialorrhoea severity in the post-assessment period with continued Xeomin treatment.	N/A.
Discontinuation rate for Xeomin	It was assumed that treatment would continue indefinitely unless discontinued due to AEs (or other reasons other than death) based on the SIAXI trial.	Feedback from UK clinical experts experienced in the treatment of sialorrhoea indicated that treatment with Xeomin would continue indefinitely unless patients discontinued due to AEs. It was therefore considered appropriate to adopt the all-cause discontinuation rates (excluding mortality) for Xeomin observed within the SIAXI trial.	Alternative discontinuation rates for Xeomin were explored in scenario analyses.
Discontinuation rate for glycopyrronium bromide plus SoC	The discontinuation rate for glycopyrronium bromide plus SoC was assumed to be 50% in the first model cycle.	Feedback from UK clinical experts experienced in the treatment of sialorrhoea indicated that treatment with glycopyrronium bromide would continue indefinitely unless patients discontinued due to AEs, and that approximately 50% of patients receiving glycopyrronium bromide would discontinue in the first 16 weeks of treatment.	Alternative discontinuation rates for glycopyrronium bromide were explored extensively in scenario analyses.
Mortality	The model assumed there to be no excess mortality associated with sialorrhoea, and no mortality differentiation between treatments	Excess mortality risk for the overall eligible patient population is unknown, hence only general population mortality was included in the base case analysis	N/A.

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AEs	It was assumed that the safety profiles of Xeomin plus SoC, glycopyrronium bromide plus SoC and SoC alone were equivalent.	In the SIAXI trial, the frequency of AEs was similar between the Xeomin treatment groups and the placebo group, so it is plausible to assume that the safety profile of Xeomin plus SoC is equivalent to that of SoC alone. It was determined that a robust ITC between Xeomin and glycopyrronium bromide, in terms of both efficacy and safety, could not be conducted. Feedback from UK clinical experts experienced in the treatment of sialorrhoea strongly suggested that treatment with glycopyrronium bromide is associated with a higher rate of AEs, so the assumption of equivalent safety profiles, and therefore equal costs associated with the management of AEs, is conservative.	N/A.
Health state costs	The model assumed that patients in the moderate and severe health states required one or two speech pathology or occupational therapy consultations each 16-week cycle, respectively.	Feedback from UK clinical experts indicated that sialorrhoea management may include one speech and language or occupational therapy consultation per 16-week cycle, and that resource use may not differ between patients with severe or moderate sialorrhoea.	Equal frequencies of consultations between the moderate and severe health states were explored in scenario analyses.

Abbreviations: AE: adverse event; LOCF: last observation carried forward; ITC: indirect treatment comparison; N/A: not applicable; SoC: standard of care; UK: United Kingdom.

B.3.7 Base case results

B.3.7.1 Base case incremental cost-effectiveness analysis results

The deterministic base case cost-effectiveness analysis results are presented in Table 57 for pairwise comparisons of Xeomin plus SoC versus glycopyrronium bromide plus SoC and SoC alone.

Given that the model assumed no mortality differentiation between treatments, all treatments were associated with the same total life-year gain, and as such, there was no incremental life-year gain for Xeomin plus SoC versus either comparator. The impact of Xeomin on improving sialorrhoea severity resulted in a lower proportion of patients residing in the lower severity health states over the modelled time horizon. Therefore, Xeomin plus SoC was associated with higher QALYs than both glycopyrronium bromide plus SoC and SoC alone, with an incremental QALY gain of 0.25 and 0.11, respectively. As well as providing higher QALYs, Xeomin plus SoC was associated with lower total costs over the model time horizon compared to glycopyrronium bromide plus SoC, but higher total costs compared to SoC alone. Thus, in the base case

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analysis, Xeomin plus SoC dominated glycopyrronium bromide plus SoC, and was associated with an incremental cost per QALY of £7,840 versus SoC alone.

Clinical outcomes predicted by the model, and a summary of the disaggregated costs and QALYs per health state are presented in Appendix J.

Table 57: Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER for Xeomin versus comparator (£/QALY)
Xeomin plus Soc	£5,875	8.18	3.38	-	-	-	-
Glycopyrronium bromide plus SoC	£14,571	8.18	3.12	-£8,696	0.00	0.25	Xeomin plus SoC dominant
SoC alone	£2,652	8.18	2.97	£3,223	0.00	0.41	£7,840

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr.: incremental; LYG: life years gained; QALYs: quality-adjusted life years.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted using a Monte-Carlo simulation with 1,000 iterations. In each iteration, the model inputs were randomly drawn from the specified distributions, as summarised in Table 58.

Whenever available, the standard error (or standard deviation if standard error could not be calculated) of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on the variability around a particular value, it was varied by ±20%. The algorithm defined by Ren et al. (2018) was used in order to generate randomly sampled health state utility values where the ordering of utility values was preserved (i.e. mild > moderate > severe).[71]

Table 58: Probability sensitivity analysis parameters and distributions

Parameter	Distribution	Mean	SE
Starting age	Gamma	65.2	11.40
Gender split (% male)	Beta	71%	0.14
Discount rate - costs	Beta	3.50%	0.01
Discount rate - benefits	Beta	3.50%	0.01
Risk ratio of death	Gamma	1.00	0.20
Drug acquisition cost per cycle - Xeomin plus SoC	Gamma	£129.90	25.98
Drug acquisition cost per cycle - Glycopyrronium bromide plus SoC	Gamma	£1,517.60	303.52
Drug acquisition cost per cycle - SoC	Gamma	£0.00	0.00
Drug administration cost per cycle - Xeomin plus SoC	Gamma	£133.51	26.70

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Drug administration cost per cycle - Glycopyrronium bromide plus SoC	Gamma	£0.00	0.00
Drug administration cost per cycle - SoC	Gamma	£0.00	0.00
Disease management costs - Severe sialorrhoea (DSFS 9-7)	Gamma	£88.41	17.68
Disease management costs - Moderate sialorrhoea (DSFS 6-4)	Gamma	£88.41	17.68
Disease management costs - Mild / no sialorrhoea (DSFS 3-2)	Gamma	£0.00	0.00
Disease management costs - Baseline for those who discontinue	Gamma	£88.41	17.68
Mean health state utility - Severe sialorrhoea (DSFS 9-7)	1-Gamma	0.5809	0.12
Mean health state utility - Moderate sialorrhoea (DSFS 6-4)	1-Gamma	0.6309	0.13
Mean health state utility - Mild/no sialorrhoea (DSFS 3-2)	1-Gamma	0.6713	0.13
Baseline utility (for discontinuer)	1-Gamma	0.6037	0.12
Discontinuation - Xeomin plus SoC (1st cycle)	Beta	2.70%	0.02
Discontinuation - Xeomin plus SoC (+2 cycles)	Beta	4.71%	0.04
Discontinuation - Glycopyrronium bromide plus SoC (1st cycle)	Beta	50.00%	0.10
Discontinuation - Glycopyrronium bromide plus SoC (+2 cycles)	Beta	4.71%	0.04
Discontinuation - SoC (1st cycle)	Beta	11.11%	0.05
Discontinuation - SoC (+2 cycles)	Beta	11.11%	0.05
TP between baseline and week 4 (9-7 to 9-7) - Xeomin plus SoC	Dirichlet (from Gamma)	54.55%	0.1091
TP between baseline and week 4 (9-7 to 6-4) - Xeomin plus SoC	Dirichlet (from Gamma)	45.45%	0.0909
TP between baseline and week 4 (9-7 to 3-2) - Xeomin plus SoC	Dirichlet (from Gamma)	0.00%	0.0000
TP between baseline and week 4 (6-4 to 9-7) - Xeomin plus SoC	Dirichlet (from Gamma)	0.3077	0.0615
TP between baseline and week 4 (6-4 to 6-4) - Xeomin plus SoC	Dirichlet (from Gamma)	0.5897	0.1179
TP between baseline and week 4 (6-4 to 3-2) - Xeomin plus SoC	Dirichlet (from Gamma)	0.1026	0.0205
TP between baseline and week 4 (3-2 to 9-7) - Xeomin plus SoC	Dirichlet (from Gamma)	0.0882	0.0176
TP between baseline and week 4 (3-2 to 6-4) - Xeomin plus SoC	Dirichlet (from Gamma)	0.8529	0.1706
TP between baseline and week 4 (3-2 to 3-2) - Xeomin plus SoC	Dirichlet (from Gamma)	0.0588	0.0118
TP between week 4 and week 20 (9-7 to 9-7) - Xeomin plus SoC	Dirichlet (from Gamma)	0.0000	0.0000
TP between week 4 and week 20 (9-7 to 6-4) - Xeomin plus SoC	Dirichlet (from Gamma)	0.0000	0.0000
TP between week 4 and week 20 (9-7 to 3-2) - Xeomin plus SoC	Dirichlet (from Gamma)	1.0000	0.2000

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TP between week 4 and week 20 (6-4 to 9-7) - Xeomin plus SoC	Dirichlet (from Gamma)	0.2308	0.0462
TP between week 4 and week 20 (6-4 to 6-4) - Xeomin plus SoC	Dirichlet (from Gamma)	0.6154	0.1231
TP between week 4 and week 20 (6-4 to 3-2) - Xeomin plus SoC	Dirichlet (from Gamma)	0.1538	0.0308
TP between week 4 and week 20 (3-2 to 9-7) - Xeomin plus SoC	Dirichlet (from Gamma)	0.0577	0.0115
TP between week 4 and week 20 (3-2 to 6-4) - Xeomin plus SoC	Dirichlet (from Gamma)	0.7500	0.1500
TP between week 4 and week 20 (3-2 to 3-2) - Xeomin plus SoC	Dirichlet (from Gamma)	0.1923	0.0385
TP between week 20 and week 36 (9-7 to 9-7) - Xeomin plus SoC	Dirichlet (from Gamma)	0.0000	0.0000
TP between week 20 and week 36 (9-7 to 6-4) - Xeomin plus SoC	Dirichlet (from Gamma)	0.5000	0.1000
TP between week 20 and week 36 (9-7 to 3-2) - Xeomin plus SoC	Dirichlet (from Gamma)	0.5000	0.1000
TP between week 20 and week 36 (6-4 to 9-7) - Xeomin plus SoC	Dirichlet (from Gamma)	0.6667	0.1333
TP between week 20 and week 36 (6-4 to 6-4) - Xeomin plus SoC	Dirichlet (from Gamma)	0.3333	0.0667
TP between week 20 and week 36 (6-4 to 3-2) - Xeomin plus SoC	Dirichlet (from Gamma)	0.0000	0.0000
TP between week 20 and week 36 (3-2 to 9-7) - Xeomin plus SoC	Dirichlet (from Gamma)	0.0000	0.0000
TP between week 20 and week 36 (3-2 to 6-4) - Xeomin plus SoC	Dirichlet (from Gamma)	0.7083	0.1417
TP between week 20 and week 36 (3-2 to 3-2) - Xeomin plus SoC	Dirichlet (from Gamma)	0.2917	0.0583
TP between week 36 and week 52 (9-7 to 9-7) - Xeomin plus SoC	Dirichlet (from Gamma)	0.0714	0.0143
TP between week 36 and week 52 (9-7 to 6-4) - Xeomin plus SoC	Dirichlet (from Gamma)	0.5000	0.1000
TP between week 36 and week 52 (9-7 to 3-2) - Xeomin plus SoC	Dirichlet (from Gamma)	0.4286	0.0857
TP between week 36 and week 52 (6-4 to 9-7) - Xeomin plus SoC	Dirichlet (from Gamma)	0.8000	0.1600
TP between week 36 and week 52 (6-4 to 6-4) - Xeomin plus SoC	Dirichlet (from Gamma)	0.2000	0.0400
TP between week 36 and week 52 (6-4 to 3-2) - Xeomin plus SoC	Dirichlet (from Gamma)	0.0000	0.0000
TP between week 36 and week 52 (3-2 to 9-7) - Xeomin plus SoC	Dirichlet (from Gamma)	0.0513	0.0103
TP between week 36 and week 52 (3-2 to 6-4) - Xeomin plus SoC	Dirichlet (from Gamma)	0.5641	0.1128
TP between week 36 and week 52 (3-2 to 3-2) - Xeomin plus SoC	Dirichlet (from Gamma)	0.3846	0.0769
TP between baseline and week 4 (9-7 to 9-7) - SoC	Dirichlet (from Gamma)	0.0000	0.0000

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TP between baseline and week 4 (9-7 to 6-4) - SoC	Dirichlet (from Gamma)	0.1667	0.0333
TP between baseline and week 4 (9-7 to 3-2) - SoC	Dirichlet (from Gamma)	0.8333	0.1667
TP between baseline and week 4 (6-4 to 9-7) - SoC	Dirichlet (from Gamma)	0.7000	0.1400
TP between baseline and week 4 (6-4 to 6-4) - SoC	Dirichlet (from Gamma)	0.3000	0.0600
TP between baseline and week 4 (6-4 to 3-2) - SoC	Dirichlet (from Gamma)	0.0000	0.0000
TP between baseline and week 4 (3-2 to 9-7) - SoC	Dirichlet (from Gamma)	0.1250	0.0250
TP between baseline and week 4 (3-2 to 6-4) - SoC	Dirichlet (from Gamma)	0.8750	0.1750
TP between baseline and week 4 (3-2 to 3-2) - SoC	Dirichlet (from Gamma)	0.0000	0.0000
Extrapolated TP (9-7 to 9-7) - all treatments	Dirichlet (from Gamma)	0.0000	0.0000
Extrapolated TP (9-7 to 6-4) - all treatments	Dirichlet (from Gamma)	0.0000	0.0000
Extrapolated TP (9-7 to 3-2) - all treatments	Dirichlet (from Gamma)	1.0000	0.2000
Extrapolated TP (6-4 to 9-7) - all treatments	Dirichlet (from Gamma)	1.0000	0.2000
Extrapolated TP (6-4 to 6-4) - all treatments	Dirichlet (from Gamma)	0.0000	0.0000
Extrapolated TP (6-4 to 3-2) - all treatments	Dirichlet (from Gamma)	0.0000	0.0000
Extrapolated TP (3-2 to 9-7) - all treatments	Dirichlet (from Gamma)	0.0000	0.0000
Extrapolated TP (3-2 to 6-4) - all treatments	Dirichlet (from Gamma)	1.0000	0.2000
Extrapolated TP (3-2 to 3-2) - all treatments	Dirichlet (from Gamma)	0.0000	0.0000

Abbreviations: DSFS: Drooling Severity and Frequency Scale; SoC: standard of care; TP transition probability.

The results of the PSA (1,000 iterations) are presented in Table 59. The probabilistic results (that take into account the combined uncertainty across model parameters) are similar to those estimated in the deterministic base case analysis, confirming the robustness of the base case analysis.

Table 59: Base case results (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Xeomin plus SoC	£5,865.46	3.28			
Glycopyrronium bromide plus SoC	£15,153.76	2.99	-£9,288.30	0.29	Xeomin plus SoC dominant
SoC alone	£2,526.91	2.82	£3,338.54	0.46	£7,258

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr.: incremental; LYG: life years gained; QALYs: quality-adjusted life years.

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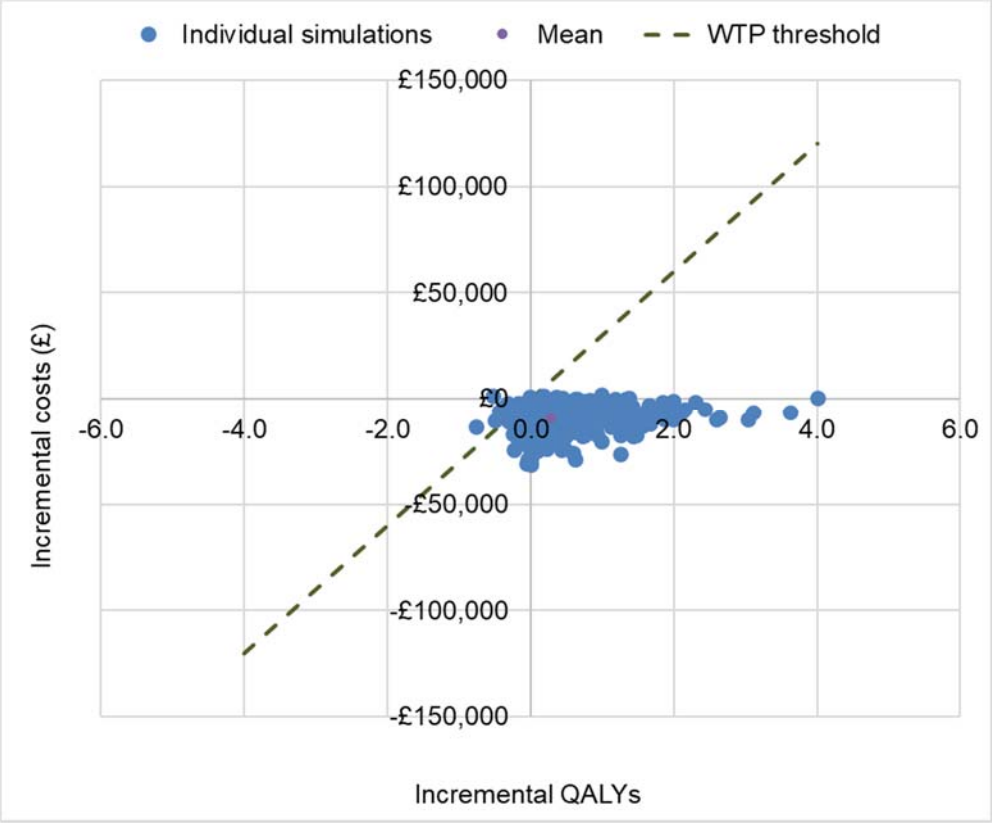
Scatter plots showing the incremental costs and QALYs for Xeomin plus SoC versus glycopyrronium bromide plus SoC and SoC alone are presented in Figure 12 and Figure 13 respectively. Assuming a willingness-to-pay threshold of £30,000 per QALY gained, the probability of Xeomin plus SoC being the most cost-effective treatment option was 64%. Cost-effectiveness acceptability curves for all therapies are presented in Figure 14.

Figure 12: Cost-effectiveness plane for Xeomin plus SoC versus glycopyrronium bromide plus SoC



Abbreviations: QALY: quality-adjusted life years; SoC: standard of care.

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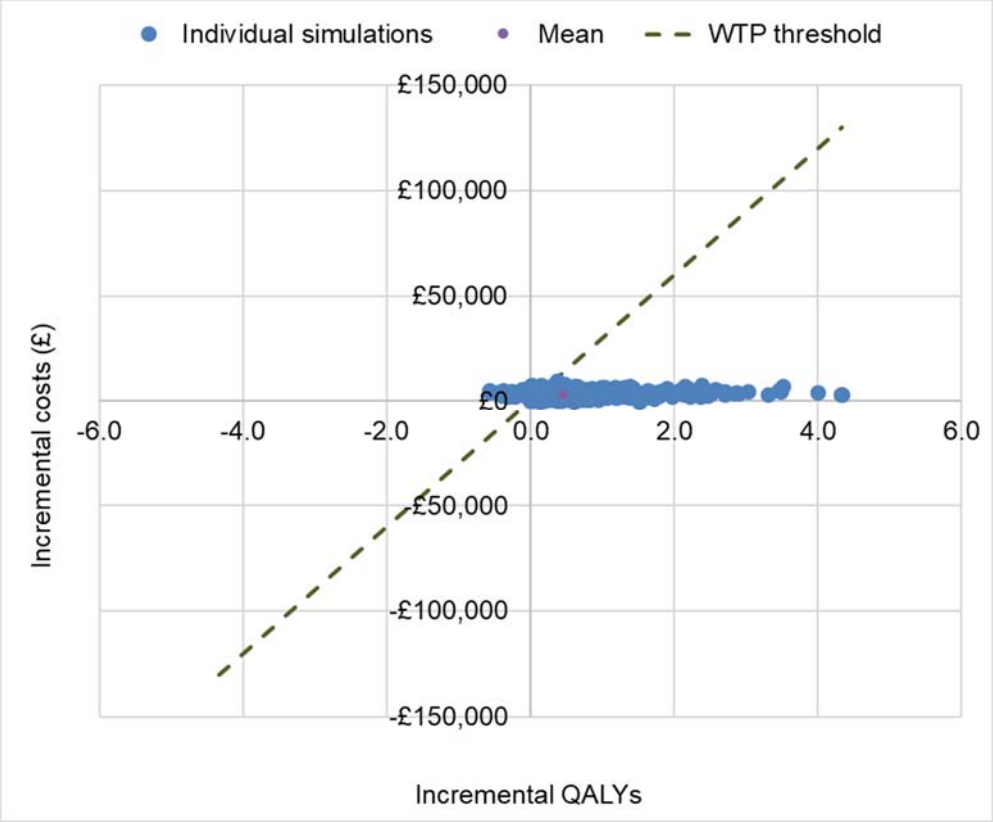
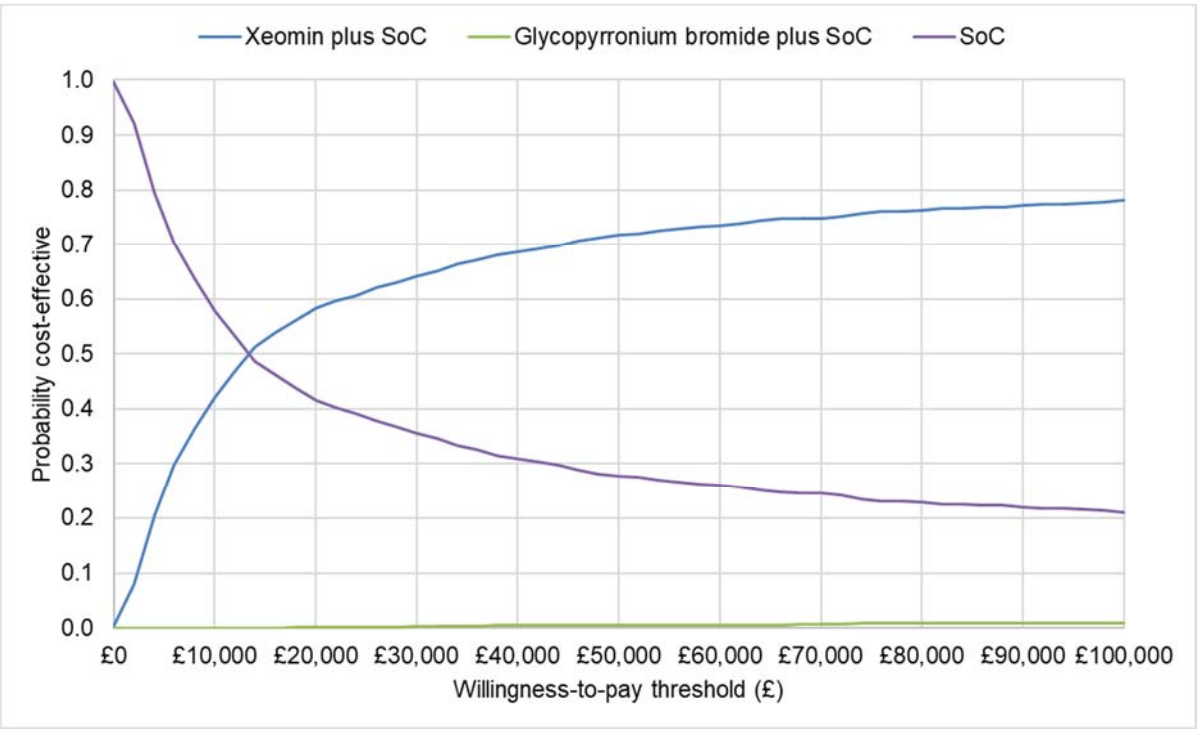
Figure 13: Cost-effectiveness plane for Xeomin plus SoC versus SoC alone



Abbreviations: QALY: quality-adjusted life years; WTP: willingness-to-pay.

Figure 14: Cost-effectiveness acceptability curve for Xeomin plus Soc versus glycopyrronium bromide plus SoC and SoC alone



Abbreviations: SoC: standard of care.

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B.3.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) was conducted by varying all parameters for which there were single input values in the model. Whenever available, values were varied using confidence intervals obtained directly from the same data source that informed the mean value. In the absence of data on the variability around a particular value, it was varied by ±20%. The DSA inputs are summarised in Table 60 below.

Table 60: Summary of DSA inputs

Parameter	Base case input	One-way SA inputs		Variation
		Lower value	Upper value	
Starting age	65	42.9	87.5	CI
Gender split (% male)	71%	56.56%	84.84%	±20%
Risk ratio of death	1.00	0.80	1.20	±20%
Drug acquisition cost per cycle - Xeomin plus SoC	£129.90	£103.92	£155.88	±20%
Drug acquisition cost per cycle - Glycopyrronium bromide plus SoC	£1,517.60	£1,214.08	£1,821.12	±20%
Drug acquisition cost per cycle - SoC	£0.00	£0.00	£0.00	±20%
Drug administration cost per cycle - Xeomin plus SoC	£133.51	£106.80	£160.21	±20%
Drug administration cost per cycle - Glycopyrronium bromide plus SoC	£0.00	£0.00	£0.00	±20%
Drug administration cost per cycle - SoC	£0.00	£0.00	£0.00	±20%
Disease management costs - Severe sialorrhoea (DSFS 9-7)	£88.41	£70.73	£106.10	±20%
Disease management costs - Moderate sialorrhoea (DSFS 6-4)	£88.41	£70.73	£106.10	±20%
Disease management costs - Mild / no sialorrhoea (DSFS 3-2)	£0.00	£0.00	£0.00	±20%
Disease management costs - Baseline for those who discontinue	£88.41	£70.73	£106.10	±20%
Mean health state utility - Severe sialorrhoea (DSFS 9-7)	0.5809	0.46	0.6309	±20%[a]
Mean health state utility - Moderate sialorrhoea (DSFS 6-4)	0.6309	0.5809	0.6713	±20%[a]
Mean health state utility - Mild/no sialorrhoea (DSFS 3-2)	0.6713	0.6309	0.8056	±20%[a]
Discontinuation - Xeomin plus SoC (1st cycle)	2.70%	0.00%	6.40%	CI
Discontinuation - Xeomin plus SoC (+2 cycles)	4.71%	0.00%	12.16%	CI
Discontinuation - Glycopyrronium bromide plus SoC (1st cycle)	50.00%	40.00%	60.00%	±20%

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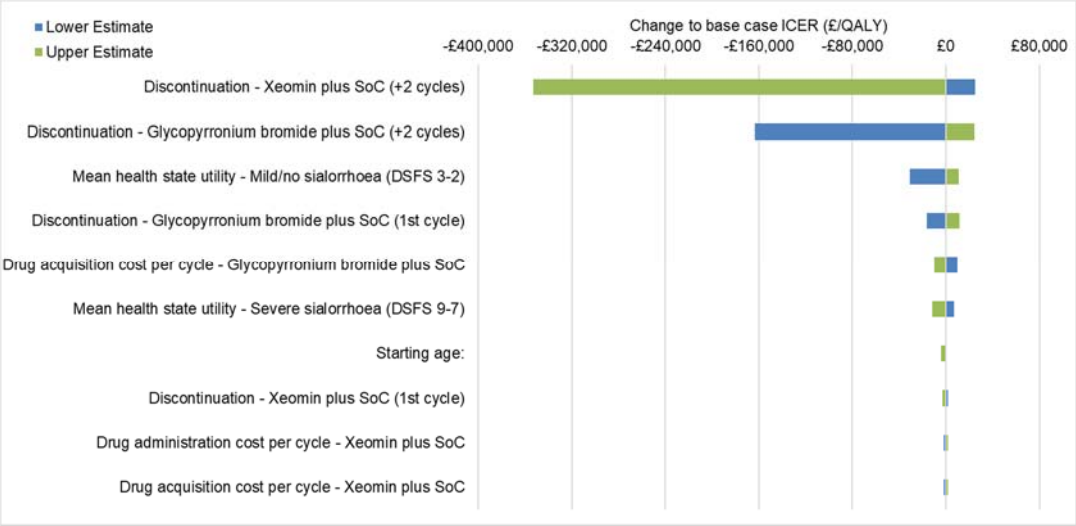
Discontinuation - Glycopyrronium bromide plus SoC (+2 cycles)	4.71%	0.00%	12.16%	CI
Discontinuation - SoC (1st cycle)	5.00%	0.85%	21.38%	CI
Discontinuation - SoC (+2 cycles)	5.00%	0.85%	21.38%	CI

[a] Given that there is a fixed order of health state utility variables, upper and lower values were bound by the utility value of the adjacent health states.
Abbreviations: CI: confidence interval; DSFS: Drooling Severity and Frequency Scale; SoC: standard of care.

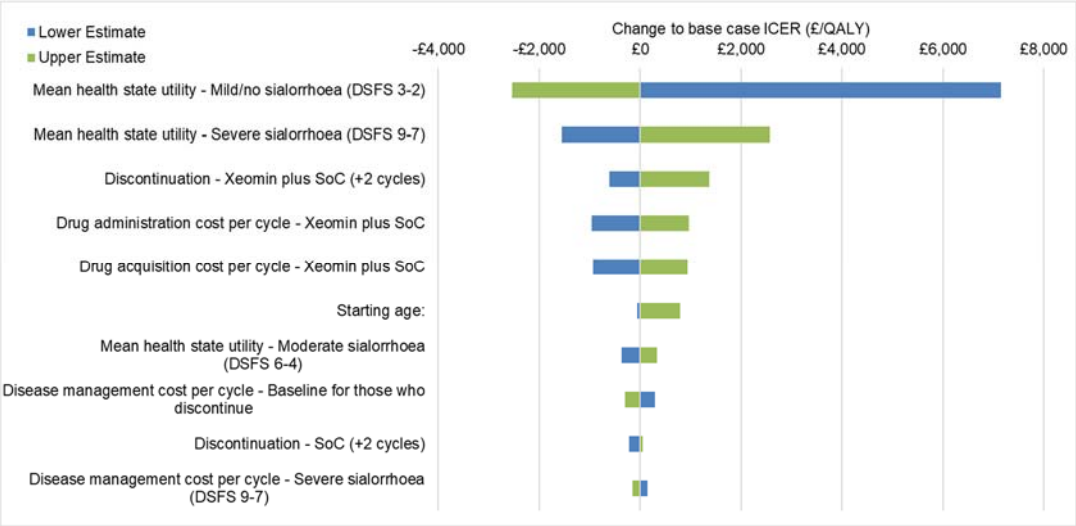
Tornado diagrams showing the top ten drivers of cost-effectiveness in the comparison of Xeomin plus SoC versus glycopyrronium plus SoC and SoC alone are presented in Figure 15 and Figure 16 respectively. Across these plots it can be seen that the most influential parameters included in the DSA in the comparison of Xeomin plus SoC versus glycopyrronium bromide plus SoC were the discontinuation rates for glycopyrronium bromide plus SoC and Xeomin plus SoC. For the comparison of Xeomin plus SoC versus SoC alone, the most influential parameters in the DSA were the health state utility values for the mild/resolved and severe health states.

Figure 15: Deterministic sensitivity analysis – tornado diagram of the top ten most influential parameters versus glycopyrronium bromide plus SoC



Abbreviations: DSFS: Drooling Severity and Frequency Scale; SoC: standard of care.

Figure 16: Deterministic sensitivity analysis – tornado diagram of the top ten most influential parameters versus SoC alone



Abbreviations: DSFS: Drooling Severity and Frequency Scale; SoC: standard of care.

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B.3.8.3 Scenario analysis

Various scenario analyses were conducted to explore the impact of assumptions that were included in the base case analysis and the results of these scenarios are presented from Table 61 to Table 68.

Time horizon

As discussed in Section B.3.2.2, a 10-year time horizon was considered an appropriate duration over which to fully capture the costs and benefits of Xeomin without introducing unnecessary extrapolation-related uncertainties, and thus was employed in the base case. Scenario analyses where the time horizon was varied are presented in Table 61. It is acknowledged that sialorrhoea is a chronic condition, therefore a scenario analysis exploring a lifetime time horizon (114 model cycles, with patients reaching 99.77 years of age) was conducted. Across all of the scenarios conducted, Xeomin was associated with an ICER of less than £10,000 per QALY gained.

Table 61: Time horizon scenarios

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incr. costs	Incr. QALYs	ICER (£/QALY)
Base case: 10-year time horizon					
Xeomin plus SoC	£5,875	3.38	-		
Glycopyrronium plus SoC	£14,571	3.12	-£8,696	0.25	Xeomin plus SoC dominant
SoC alone	£2,652	2.97	£3,223	0.41	£7,840
Scenario: 2-year time horizon					
Xeomin plus SoC	£2,112	0.90	-		
Glycopyrronium plus SoC	£6,062	0.82	-£3,950	0.09	Xeomin plus SoC dominant
SoC alone	£789	0.77	£1,324	0.13	£9,831
Scenario: 5-year time horizon					
Xeomin plus SoC	£4,047	2.02	-		
Glycopyrronium plus SoC	£10,765	1.84	-£6,718	0.18	Xeomin plus SoC dominant
SoC alone	£1,635	1.73	£2,411	0.29	£8,208
Scenario: 20-year time horizon					
Xeomin plus SoC	£7,454	4.93	-		
Glycopyrronium plus SoC	£17,032	4.65	-£9,578	0.28	Xeomin plus SoC dominant
SoC alone	£3,860	4.47	£3,595	0.46	£7,743
Scenario: 30-year time horizon					
Xeomin plus SoC	£7,846	5.39	-	-	-
Glycopyrronium plus SoC	£17,488	5.11	-£9,642	0.29	Xeomin plus SoC dominant
SoC alone	£4,225	4.93	£3,622	0.47	£7,738
Scenario: lifetime time horizon					
Xeomin plus SoC	£7,868	5.42	-	-	-
Glycopyrronium plus SoC	£17,511	5.13	-£9,643	0.29	Xeomin plus SoC dominant

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SoC alone	£4,246	4.95	£3,622	0.47	£7,738

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care.

Comparator efficacy

As discussed in Section B.2.9, due to the limitations of the evidence base, an indirect treatment comparison versus glycopyrronium bromide was not possible. Feedback from UK clinical experts strongly suggested that glycopyrronium bromide is far inferior to Xeomin in reducing sialorrhoea severity.[1] Furthermore, in an analysis conducted by NICE for the clinical guideline of cerebral palsy in under 25s, glycopyrronium bromide was considered to be less effective than botulinum toxin type A, and was associated with a mean improvement in drooling score of 3, compared with botulinum toxin type A which was assigned a mean improvement in drooling score of 4.[25] As such, in the absence of an alternative approach, the base case analysis employed data for patients in the Xeomin 100 U arm of the SIAXI trial to represent the effectiveness of glycopyrronium bromide plus SoC in the model, but reduced by 25%.

Given the uncertainty associated with this approach, a scenario analysis was also conducted within which it was assumed that the efficacy of glycopyrronium bromide was equivalent to that of Xeomin and the results are presented in Table 62. This assumption of equal efficacy is considered to be highly conservative, likely resulting in an overestimate of the ICER for Xeomin versus glycopyrronium bromide.

Despite the assumption of equivalent efficacy for Xeomin plus SoC and glycopyrronium bromide plus SoC, the higher discontinuation rate in the first model cycle for the comparator resulted in a lower proportion of patients residing in the lower severity health states over the modelled time horizon. Therefore, Xeomin plus SoC was associated with higher QALYs than glycopyrronium bromide plus SoC, with an incremental QALY gain of 0.21, and remained dominant versus this comparator.

Table 62: Scenarios involving alternative comparator efficacy

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incr. costs	Incr. QALYs	ICER (£/QALY)
Base case: versus glycopyrronium bromide plus SoC					
Xeomin plus SoC	£5,875	3.38	-		
Glycopyrronium plus SoC	£14,571	3.12	-£8,696	0.25	Xeomin plus SoC dominant
Scenario: equal efficacy between glycopyrronium bromide plus SoC and Xeomin plus SoC					
Xeomin plus SoC	£5,875	3.38			
Glycopyrronium plus SoC	£14,475	3.16	-£8,600	0.21	Xeomin plus SoC dominant

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care.

Alternative anticholinergic therapies

Feedback from UK clinical experts suggested that oral glycopyrronium bromide is one of the most commonly tried anticholinergic therapies for the treatment of sialorrhoea in UK clinical practice, and was considered the most relevant comparator to Xeomin in the context of this appraisal to include in the base case analysis.[1] However, given transdermal hyoscine hydrobromide and sublingual atropine may also be used in some patients, scenario analyses

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versus these therapies are presented in Table 64.[1] In these scenarios, it has been assumed that clinical inputs (efficacy and discontinuation rates) are consistent across anticholinergic therapies, and as such the incremental QALYs were equivalent to those observed for glycopyrronium bromide plus SoC. Treatment acquisition costs for hyoscine hydrobromide plus SoC and atropine sulfate plus SoC are presented in Table 63.

Compared with glycopyrronium bromide, both hyoscine hydrobromide and atropine sulfate were associated with substantially lower total costs, and thus Xeomin plus SoC was associated with an incremental cost per QALY of £6,599 and £10,760 versus hyoscine hydrobromide plus SoC and atropine sulfate plus SoC, respectively. It is important to note that, as for glycopyrronium bromide, due to the limitations of the evidence base, no indirect treatment comparisons versus any of the anticholinergic therapies were possible; it was therefore assumed that the efficacy of the anticholinergic comparators was equivalent.

Table 63: Unit costs associated with alternative anticholinergic therapies

Intervention/ comparator	Defined dosing[a]	Price per pack or vial[b]	Cost per dose	Administration cost per dose	Frequency per cycle	Total cost per cycle
Hyoscine hydrobromide plus SoC	1.5 mg every 72 hours	2 x 1.5mg patches: £12.87	£6.44	£0.00	37.3	£240.24
Atropine sulfate plus SoC	0.75 mg daily	10 ml x 10 mg/ml eye drops: £131.92	£0.99	£0.00	112	£110.81

[a] The dosing schedule for hyoscine hydrobromide was based on Mato *et al.* (2010) and Odachi *et al.* (2017); the dosing schedule for atropine sulfate was based on Thomas et al. (2012). [b] List prices of hyoscine hydrobromide and atropine sulfate were taken from the BNF online (2019).
Abbreviations: BNF: British National Formulary; SoC: standard of care.

Table 64: Scenarios involving alternative anticholinergic therapies

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incr. costs	Incr. QALYs	ICER (£/QALY)
Base case: versus glycopyrronium bromide plus SoC					
Xeomin plus SoC	£5,875	3.38	-		
Glycopyrronium plus SoC	£14,571	3.12	-£8,696	0.25	Xeomin plus SoC dominant
Scenario: versus hyoscine hydrobromide plus SoC					
Xeomin plus SoC	£5,875	3.38	-		
Hyoscine hydrobromide plus SoC	£4,211	3.12	£1,665	0.25	£6,599
Scenario: versus atropine sulfate plus SoC					
Xeomin plus SoC	£5,875	3.38	-		
Atropine sulfate plus SoC	£3,161	3.12	£2,715	0.25	£10,760

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care.

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Alternative discontinuation rates

Scenario analyses using alternative discontinuation rates for the intervention and comparators are presented in Table 65.

Feedback from UK clinical experts experienced in the treatment of sialorrhoea indicated that treatment with Xeomin would continue indefinitely unless patients discontinued due to AEs; the discontinuation rates for Xeomin plus SoC were therefore based on data from the SIAXI trial.[1] Increasing or decreasing the discontinuation rates for Xeomin plus SoC did not result in a material change in the ICER versus or SoC alone, and Xeomin plus SoC still dominated glycopyrronium bromide plus SoC.

Feedback from UK clinical experts indicated that treatment with glycopyrronium bromide would continue indefinitely unless patients discontinued due to AEs, and that approximately 50% of patients receiving glycopyrronium bromide would discontinue in the first 16 weeks of treatment.[1] Xeomin plus SoC remained dominant across the majority of scenarios where the discontinuation rates for glycopyrronium bromide were varied.

Scenarios were conducted where no discontinuation rates for SoC alone were applied in the model. As discussed in Section B.3.3.4, this scenario implicitly assumes that improvements observed in the placebo arm of the SIAXI trial, which are at least in part due to the placebo effect, are maintained across the entire model time horizon. However, this only resulted in a minimal increase in the ICER versus SoC alone.

Table 65: Discontinuation rate scenarios

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incr. costs	Inc. QALYs	ICER (£/QALY)
Base case: See section B.3.3.4					
Xeomin plus SoC	£5,875	3.38	-		
Glycopyrronium plus SoC	£14,571	3.12	-£8,696	0.25	Xeomin plus SoC dominant
SoC alone	£2,652	2.97	£3,223	0.41	£7,840
Scenario: no discontinuation rate for Xeomin plus SoC in all model cycles					
Xeomin plus SoC	£8,571	3.78	-		
Glycopyrronium plus SoC	£14,571	3.12	-£6,000	0.66	Xeomin plus SoC dominant
SoC alone	£2,652	2.97	£5,919	0.82	£7,228
Scenario: discontinuation rate of 10% for Xeomin plus SoC in all model cycles					
Xeomin plus SoC	£4,494	3.17	-		
Glycopyrronium plus SoC	£14,571	3.12	-£10,077	0.05	Xeomin plus SoC dominant
SoC alone	£2,652	2.97	£1,842	0.21	£8,852
Scenario: discontinuation rate of 25% for glycopyrronium bromide plus SoC in the first model cycle; base case discontinuation in subsequent cycles					
Xeomin plus SoC	£5,875	3.38	-		
Glycopyrronium plus SoC	£19,910	3.22	-£14,035	0.16	Xeomin plus SoC dominant
Scenario: discontinuation rate of 25% for glycopyrronium bromide plus SoC in all model cycles					

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Xeomin plus SoC	£5,875	3.38	-		
Glycopyrronium plus SoC	£8,263	3.00	-£2,388	0.38	Xeomin plus SoC dominant
Scenario: discontinuation rate of 50% for glycopyrronium bromide plus SoC in all model cycles					
Xeomin plus SoC	£5,875	3.38	-		
Glycopyrronium plus SoC	£5,400	2.95	£476	0.42	£1,123
Scenario: discontinuation rate of 75% for glycopyrronium bromide plus SoC in the first model cycle; base case discontinuation in subsequent cycles					
Xeomin plus SoC	£5,875	3.38	-		
Glycopyrronium plus SoC	£9,232	3.03	-£3,357	0.35	Xeomin plus SoC dominant
Scenario: discontinuation rate of 75% for glycopyrronium bromide plus SoC in all model cycles					
Xeomin plus SoC	£5,875	3.38	-		
Glycopyrronium plus SoC	£4,401	2.94	£1,474	0.44	£3,379
Scenario: no discontinuation rate for SoC alone in all model cycles					
Xeomin plus SoC	£5,875	3.38	-		
SoC alone	£3,388	3.05	£2,487	0.33	£7,501

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care.

Alternative health state utility values

As discussed in Section B.3.4.5, in the base case analysis, the health state utility values were based on the hypothetical utility values reported in the NICE guideline for cerebral palsy in under 25s (NG62). This was because the results of the LCMM predicted a difference of only 0.0423 and 0.0543 between the utility of the mild/resolved versus moderate and the mild/resolved versus severe health states, respectively, which was not considered clinically plausible in terms of accurately reflecting the differences in HRQoL expected given the differences in disease severity. Nevertheless a scenario analysis using the LCMM analysis was conducted to demonstrate the impact on the ICER. The results of a scenario analysis adopting the utility values derived from the LCMM analysis of patient-level EQ-5D index scores and DSFS sum scores from the SIAXI trial are presented in Table 66.

Table 66: Scenarios involving alternative health state utility values

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incremental costs	Incremental QALYs	ICER (£/QALY)
Base case: health state utility values estimated using NG62					
Xeomin plus SoC	£5,875	3.38	-		
Glycopyrronium plus SoC	£14,571	3.12	-£8,696	0.25	Xeomin plus SoC dominant
SoC alone	£2,652	2.97	£3,223	0.41	£7,840
Scenario: health state utility values estimated using the LCMM analysis					

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Xeomin plus SoC	£5,875	4.94	-		
Glycopyrronium plus SoC	£14,571	4.88	-£8,696	0.06	Xeomin plus SoC dominant
SoC alone	£2,652	4.84	£3,223	0.10	£32,793

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care.

Alternative mortality input scenarios

Excess mortality risk for the overall eligible patient population is unknown. The impact of applying excess mortality due to underlying aetiology was explored by applying a standardised mortality ratio (SMR) of 1.92, calculated for a UK population of patients with Parkinson's disease by Hobson *et al.* (2017).[72] Applying the SMR resulted in a very minimal change in the ICER versus or SoC alone, and Xeomin plus SoC still dominated glycopyrronium bromide plus SoC.

Table 67: Mortality input scenarios

Intervention	Total Costs (discounted)	Total QALYs (discounted)	Incremental costs	Incremental QALYs	ICER (£/QALY)
Base case: no excess mortality					
Xeomin plus SoC	£5,875	3.38	-		
Glycopyrronium plus SoC	£14,571	3.12	-£8,696	0.25	Xeomin plus SoC dominant
SoC alone	£2,652	2.97	£3,223	0.41	£7,840
Scenario: SMR of 1.92 applied, based on Hobson *et al.* (2017)					
Xeomin plus SoC	£5,606	3.19	-		
Glycopyrronium plus SoC	£13,987	2.95	-£8,381	0.24	Xeomin plus SoC dominant
SoC alone	£2,508	2.79	£3,098	0.39	£7,903

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care; SMR: standard mortality rate.

Alternative resource use inputs

The base case analysis assumed that the resource use associated with the severe sialorrhoea health state would be greater than that required for the moderate sialorrhoea health state.

Feedback from UK clinical experts suggested that sialorrhoea management may include one speech and language or occupational therapy consultation per 16-week cycle, and that resource use may not differ between patients with severe or moderate sialorrhoea, hence a scenario analysis was conducted based on this assumption. Assuming an equal frequency of consultations between health states did not result in a material change in the ICER versus or SoC alone, and Xeomin plus SoC still dominated glycopyrronium bromide plus SoC.

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Table 68: Scenarios involving alternative resource use

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incremental costs	Incremental QALYs	ICER (£/QALY)
Base case: one consultation per cycle for moderate/two consultations per cycle for severe					
Xeomin plus SoC	£5,875	3.38	-		
Glycopyrronium plus SoC	£14,571	3.12	-£8,696	0.25	Xeomin plus SoC dominant
SoC alone	£2,652	2.97	£3,223	0.41	£7,840
Scenario: one consultation per cycle for both health states					
Xeomin plus SoC	£5,730	3.38	-		
Glycopyrronium plus SoC	£14,453	3.12	-£8,724	0.25	Xeomin plus SoC dominant
SoC alone	£2,352	2.97	£3,378	0.41	£8,217

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care.

B.3.8.4 Summary of sensitivity analyses results

Results of the sensitivity analyses demonstrate that the base case cost-effectiveness results exhibit little variation when the combined distributional uncertainty across model parameters is taken into account (PSA) as well as for the majority of changes to the modelling approach that were explored in scenario analyses. The DSA demonstrated that the most influential parameters driving the model were the discontinuation rates for glycopyrronium bromide plus SoC and Xeomin plus SoC and health state utility values, versus glycopyrronium bromide plus SoC and SoC alone, respectively. Across almost all of the scenarios conducted, Xeomin either dominated glycopyrronium bromide plus SoC or was associated with ICERs versus both glycopyrronium bromide plus SoC or SoC alone of less than £20,000 per QALY gained.

B.3.9 Subgroup analysis

No economic subgroup analyses were conducted as part of this appraisal.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Clinician input was sought during the development of the UK cost-effectiveness model to ensure that the inputs and assumptions used in the base case analysis were relevant to UK clinical practice to validate the clinical plausibility of the outcomes predicted by the model.

In particular, clinician feedback was used to guide the choice of anticholinergic comparators and the assumptions surrounding comparator efficacy. Expert clinical opinion was also sought to validate other inputs and assumptions such as the baseline characteristics of the modelled cohort, the discontinuation rate for Xeomin and glycopyrronium bromide plus SoC, health state resource use and mortality.

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B.3.11 Interpretation and conclusions of economic evidence

Chronic sialorrhoea is an extremely debilitating disorder that can have a considerable psychosocial impact on patients through social embarrassment and decreased self-esteem, which can lead to social isolation.[12, 18] As a result, sialorrhoea can have a detrimental effect on the QoL of both patients and carers. Clinically, the development of sialorrhoea can lead to a variety of negative sequelae including perioral dermatitis, poor oral hygiene, bad breath, increased amount of intra-oral occult bacteria, eating and speaking difficulty, sleep disturbance, dehydration and fatigue.[12, 15, 17] Furthermore, the anterior loss of saliva may also cause saliva to pool at the back of the throat which, in addition to contributing to the sensation of choking and anxiety, can lead to the development of life-threatening aspiration pneumonia if saliva is inhaled.[15, 18]

Current treatment for chronic sialorrhoea is limited; many patients do not receive active therapy, and their sialorrhoea is instead managed with basic non-pharmacological management (SoC), which may include practical aids, such as bibs, as well as speech, language and occupational therapy.[1] For patients who do receive active therapy, one of the most commonly prescribed therapies is oral glycopyrronium bromide, which is associated with numerous unwanted effects in other organ systems, including urinary retention, constipation, increased intraocular pressure, cessation of perspiration with increased body temperature and double vision.[15, 29, 30]

The efficacy of Xeomin as a treatment for chronic sialorrhoea has been demonstrated in the SIAXI trial, a large, multicentre, RCT, where treatment with Xeomin resulted in consistent, significant reductions in salivary flow rate (uSFR), leading to consistent, positive and clinically relevant improvements in sialorrhoea (GICS, response rate, DSFS, mROMP). In contrast to anticholinergic therapies, Xeomin is administered as localised injections, which may reduce the likelihood of off-target effects. This is corroborated by evidence from the SIAXI trial, where the frequency of AEs was similar between patients receiving active Xeomin treatment and placebo (in the MP, 45.9% and 43.2% of patients experienced any TEAE in the Xeomin 100U and 75U groups, respectively, compared with 41.7% of patients in the placebo group).

Whilst a direct comparison could not be made versus glycopyrronium bromide in terms of efficacy or safety, feedback from UK clinical experts experienced in the treatment of sialorrhoea was that the efficacy of glycopyrronium bromide is by far inferior to that of Xeomin, and there is no long-term data assessing the safety and/or efficacy of glycopyrronium bromide.[1] Furthermore, in terms of safety, feedback from UK clinical experts strongly suggested that treatment with glycopyrronium bromide is associated with a higher rate of AEs than Xeomin, particularly dry mouth, agitation/nervousness, constipation and nausea.[1]

As demonstrated in the cost-effectiveness analysis, Xeomin plus SoC was associated with higher QALYs than both glycopyrronium bromide plus SoC and SoC alone, with an incremental QALY gain of 0.25 and 0.41, respectively. As well as providing higher QALYs, Xeomin plus SoC was associated with lower total costs over the model time horizon compared to glycopyrronium bromide plus SoC, but higher total costs compared to SoC alone. Thus, in the base case analysis, Xeomin plus SoC dominated glycopyrronium bromide plus SoC, and was associated with an incremental cost per QALY of £7,840 versus SoC alone. These results were corroborated within the PSA and the multiple scenario analyses performed.

The innovative nature of Xeomin has been recognised by the US Food and Drugs Administration (FDA): Xeomin is first in its class, as the only treatment approved by the FDA for treatment of sialorrhoea (July 2018). Xeomin was also granted a priority review designation, which is

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indicative of its potential to provide significant improvements in the safety and effectiveness of the treatment for sialorrhoea.

In summary, Xeomin represents a cost-effective use of NHS resources that has the potential to provide significant, consistent improvements in sialorrhoea, whilst minimising AEs and reducing the administrative burden on patients and caregivers, for a debilitating condition with a considerable unmet need.

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B.5 Appendices

Appendix C: Summary of Product Characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Clostridium botulinum neurotoxin type A for treating chronic sialorrhoea [ID1150]

Clarification questions

February 2019

File name	Version	Contains confidential information	Date
ID1150_Xeomin_Clarification Questions [REDACTED]	1.0	Yes	15th March 2019

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Section A: Clarification on effectiveness data

A1. Priority: Please clarify further why the EQ-5D may be insensitive to health-related quality of life associated with drooling. Please critically assess each domain within the EQ-5D and comment on whether these are likely to be affected by drooling severity.

The impact of sialorrhoea on patient health-related quality of life (HRQoL) is substantial, and an improvement in sialorrhoea severity may affect many aspects of HRQoL that are covered by the EQ-5D questionnaire, as described below. However, the vast majority of patients with sialorrhoea also suffer from extremely debilitating underlying conditions which themselves have a detrimental impact on HRQoL, including Parkinson's disease, motor neurone disease, stroke or cerebral palsy, traumatic or acquired brain injury.

Therefore, whilst improvements in sialorrhoea severity are associated with meaningful HRQoL benefits for patients, the value of these improvements may be obscured by the HRQoL impact of the underlying condition and may not ultimately be recognised in terms of the EQ-5D-3L scoring system. The EQ-5D-3L measure will only register a change in patient utility where a patient is able to indicate a step-change in the level of at least one domain, e.g. in terms of allowing the patient to move from a 3 (extreme problems) to a 2 (some problems), or from a 2 (some problems) to a 1 (no problems).

Taking an example, the majority of patients enrolled within the SIAXI trial responded with a score of 2 (some problems) for all 5 domains at baseline (mobility: [redacted]%; self-care: [redacted]%; usual activities: [redacted]%; pain: [redacted]%; anxiety/depression: [redacted]%). For an improvement in HRQoL due to reduced drooling to register on the EQ-5D-3L, such patients would need to feel able to grade these domains with a score of 1 (no problems). Given the impact of their severe underlying conditions on HRQoL, many trial patients will have been highly unlikely to be able to describe "no problems" for many or all of the domains. Nevertheless, there is no doubt that improvements in sialorrhoea severity do have a positive impact on patient HRQoL, as indicated by the results of the patient's Global Impression of Change Scale (GICS) from the SIAXI trial (the LS-Mean difference between the Xeomin 100 U group and placebo group was 0.58 [SE: 0.183], representing a statistically significant difference in GICS scores between these groups [p=0.002]).

The anticipated impact of sialorrhoea improvements on HRQoL is described below in the context of each of the HRQoL domains of the EQ-5D, indicating how sialorrhoea would be expected to provide HRQoL improvements in these general domains of HRQoL which the EQ-5D-3L scoring system would be too insensitive to register.:

- *Mobility:* Whilst sialorrhoea may not inhibit a patient's mobility directly, some patients may find that once they sit upright or stand up, their sialorrhoea becomes unmanageable and they therefore do not want to mobilise e.g. attend physiotherapy sessions, through fear of excessive drooling. An improvement in sialorrhoea severity may therefore allow patients to mobilise more freely. However, a patient with stroke or severe Parkinson's disease is very unlikely to be able to indicate "no problems" with mobility, hence any such HRQoL benefit on the mobility domain for a patient who indicated a score of 2 for mobility at baseline is lost (i.e. regarded as "no change") due to the insensitivity of EQ-5D-3L in this context.
- *Self-care:* Chronic sialorrhoea may become unmanageable to the point that patients are unable to care for themselves and require a carer to help control excessive drooling e.g.

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through the application of tissues or bibs. An improvement in sialorrhoea severity may therefore allow the condition to be managed by patients themselves. However, a patient with stroke or severe Parkinson's disease is very unlikely to be able to indicate "no problems" with self-care, hence any such HRQoL benefit on the self-care domain for a patient who indicated a score of 2 for self-care at baseline is lost (i.e. regarded as "no change") due to the insensitivity of EQ-5D-3L in this context.

- *Usual activities:* Chronic sialorrhoea can have a substantial impact on patients being able to perform usual daily activities. Patients may feel anxious and embarrassed to go out in public or socialise, and excessive drooling may also discourage patients from performing certain usual activities such as reading or using electronic devices through fear of causing damage; this in turn may also impact on patients' education. However, a patient with stroke or severe Parkinson's disease is very unlikely to be able to indicate "no problems" with undertaking usual activities, hence any such HRQoL benefit on the usual activities domain for a patient who indicated a score of 2 for usual activities at baseline is lost (i.e. regarded as "no change") due to the insensitivity of EQ-5D-3L in this context.
- *Pain/discomfort:* Whilst sialorrhoea is rarely painful itself, left untreated sialorrhoea may lead to a variety of negative sequelae including perioral dermatitis, poor oral hygiene, increased amount of intra-oral occult bacteria, eating and speaking difficulty, sleep disturbance, dehydration and fatigue, all of which may cause pain or discomfort. An improvement in sialorrhoea severity would therefore reduce the discomfort associated with the adverse effects of chronic sialorrhoea. However, a patient with stroke or Parkinson's disease is very unlikely to be able to indicate "no problems" with pain or discomfort, hence any such HRQoL benefit on the pain/discomfort domain for a patient who indicated a score of 2 for pain/discomfort at baseline is lost (i.e. regarded as "no change") due to the insensitivity of EQ-5D-3L in this context.
- *Anxiety/depression:* Posterior loss of saliva may cause saliva to pool at the back of the throat which, in addition to contributing to the sensation of choking and anxiety, can lead to the development of life-threatening aspiration pneumonia if saliva is inhaled. In addition, sialorrhoea can have a considerable psychosocial impact on patients through social embarrassment and decreased self-esteem, which can lead to social isolation. An improvement in sialorrhoea severity would allow patients to eat and speak with less difficulty, as well as go out in public and socialise, without embarrassment or anxiety. However, a patient with stroke or severe Parkinson's disease is very unlikely to be able to indicate "no problems" with anxiety or depression, hence any such HRQoL benefit on the anxiety/depression domain for a patient who indicated a score of 2 for anxiety/depression at baseline is lost (i.e. regarded as "no change") due to the insensitivity of EQ-5D-3L in this context.

A2. Priority: Please clarify what proportion of EQ-5D responses were completed by the patient's carers. Please comment on whether this could affect the sensitivity of the EQ-5D to drooling symptoms

As per the SIAXI trial protocol, patients were asked to fill in the EQ-5D independently of others, except insofar as they needed help with reading or writing, in which case another person was to assist them (such help was to be recorded). If the patient was not able to answer the questions even with assistance, then this was to be documented in the eCRF; in such cases the EQ-5D was left blank.

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As such, *all* of the EQ-5D responses were *judged* by the patients themselves. No EQ-5D responses were judged by the patient's carers hence the sensitivity of the EQ-5D to sialorrhoea would not have been affected by any carer completion of the EQ-5D questionnaire. In cases where patients needed help with reading or writing, another person assisted the patient with the completion of the EQ-5D response. The proportion of EQ-5D responses that required assistance was [redacted] ([redacted]%).

A3. Priority: Please clarify the process in which patients were recruited to SIAXI. Clinical advice received by the ERG indicates that a proportion of patients may not suffer much disutility associated with drooling status. Recruiting such patients would result in little change in utility despite reduced symptoms. Please clarify whether there was a recruitment requirement for the patient to be concerned by their drooling status.

The eligibility criteria of the SIAXI trial included patients with chronic troublesome sialorrhoea related to parkinsonism or stroke or traumatic brain injury (for at least 3 months) at screening. This was defined as the presence of *all* of the following, at screening and at baseline and for at least the 3 months before screening (where retrospective responses to questionnaires were impossible, a statement of equivalent severity sufficed):

- A Drooling Severity and Frequency Scale (DSFS) sum score of at least 6 points *and*
- A score of at least 2 points for each item of the DSFS *and*
- A score of at least 3 points on the modified Radboud Oral Motor Inventory for Parkinson's disease (mROMP), Section III 'Drooling', Item A

Patients who were not concerned by their drooling status were not explicitly excluded from entry into the trial, however all patients had to meet the eligibility criteria detailed above.

A4. There are 15 studies of comparators currently classed as included in the systematic literature review. However, none of these contribute data to the review. The ERG suggests re-defining these as study design included, but data excluded. Please provide a table of these studies with the reason their data cannot be used. Note that it is possible to convert drooling scales to standardised mean difference to allow meta-analysis, as in Vashista 2013 or Sridharan 2018 or Narayanaswami 2016, so reasons need to go beyond the different scales used.

The clinical systematic literature review (SLR) identified 15 studies investigating comparator therapies that met the review eligibility criteria; all 15 studies were therefore included within the review. The 15 included studies were then taken forward to a feasibility assessment of conducting a potential network meta-analysis (NMA) to ascertain the relative effectiveness of Xeomin versus the relevant comparators oral glycopyrronium bromide and standard of care (SoC).

Full details of the feasibility assessment are presented in Section B.2.9 of the company submission. Ultimately it was not considered appropriate to conduct an NMA between the identified studies for several reasons: these were listed in the original company submission and include the heterogeneity in the patient populations in terms of severity and duration of onset of sialorrhoea, the heterogeneity in baseline characteristics, the heterogeneity in outcomes

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assessed, the timepoints at which each of these were assessed, the complexity of the cross-over study designs as well as the overall quality of the studies and the reporting of study methodology and results.

Most importantly, the outcomes measured in each of the trials differed substantially, with a different primary outcome assessed in almost every trial, each with its own measurement definition, numerical scale, and likely distribution of grades on that scale. Whilst it is acknowledged that it could be possible to convert drooling scales to standardised mean differences, the outcome of such an analysis would need to be transformed into results that could be considered clinically meaningful and also usable within the economic model e.g. such an analysis would only indicate that outcomes from treatment A are ~1 standard deviation better than outcomes from treatment B. The outcomes assessed in each of the trials, together with the key additional reasons why it was not considered appropriate to use the data from each of the 15 studies identified for comparator therapies in a potential NMA are presented below in Table 1.

Table 1: Rationale for exclusion of studies from a potential network meta-analysis

#	Citation	Outcome assessed	Further reasons for exclusion from a potential NMA
1	Arbouw M, Movig K, Koopmann M, et al. Glycopyrrolate for sialorrhea in Parkinson disease: a randomized, double-blind, crossover trial. Neurology. Volume 74, 2010:1203-1207.	Custom sialorrhoea scoring scale	Small patient numbers (n<30); Outcomes not assessed at relevant timepoints for comparison
2	Colen-De Koning JCA, Man WH, Wilting I, et al. The effect of glycopyrronium bromide on nocturnal clozapine induced sialorrhoea in psychiatric patients, 2015.	Functional Oral Intake Scale (FOIS)	Small patient numbers (n<30); Outcomes not assessed at relevant timepoints for comparison
3	Man WH, Colen-de Koning JC, Schulte PF, et al. The Effect of Glycopyrrolate on Nocturnal Sialorrhea in Patients Using Clozapine: A Randomized, Crossover, Double-Blind, Placebo-Controlled Trial. J Clin Psychopharmacol 2017;37:155-161.	Patient Global Impression of Severity (PGI-S) scale	Outcomes not assessed at relevant timepoints for comparison
4	Brodtkorb E, Wyzocka-Bakowska MM, Lillevold PE, et al. Transdermal scopolamine in drooling. Journal of Mental Deficiency Research 1988;32:233-237.	Did not use any scale, instead describing drooling as either constant or persistent	Outcome not able to be compared; Small patient numbers (n<30); Outcomes not assessed at relevant timepoints for comparison
5	Mato A, Limeres J, Tomás I, et al. Management of drooling in disabled patients with scopolamine patches. British journal of clinical pharmacology. Volume 69, 2010:684-688.	Did not use any scale, instead describing drooling as either constant or persistent	Small patient numbers (n<30); Outcomes not assessed at relevant timepoints for comparison
6	Takeuchi I, Hanya M, Uno J, et al. Effectiveness of the repeated administration of scopolamine ointment on clozapine-induced hypersalivation in patients with treatment-resistant schizophrenia: A preliminary study. Asia Pac Psychiatry 2017;9.	Did not use a scale, instead including patients described as experiencing distress caused by hypersalivation	Outcome not able to be compared
7	Odachi K, Narita Y, Machino Y, et al. Efficacy of transdermal scopolamine for sialorrhea in patients with amyotrophic lateral sclerosis. Cogent medicine. Volume 4, 2017. Odachi K, Narita Y, Machino Y, et al. Efficacy of transdermal scopolamine for	Total and saliva subscale score of the revised ALS Functional Rating Scale (ALSFRS-R)	Outcomes not assessed at relevant timepoints for comparison

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	sialorrhea in patients with amyotrophic lateral sclerosis. Journal of the Neurological Sciences 2017;381 (Supplement 1):750.		
8	Thomsen T, Galpern W, Asante A, et al. Ipratropium bromide spray as treatment for sialorrhea in Parkinson's disease. Movement disorders. Volume 22, 2007:2268-2273.	Salivation subdomain of the disease-specific Unified Parkinson's disease rating scale (UPDRS)	Drug not used in UK clinical practice; Outcomes not assessed at relevant timepoints for comparison
9	Sockalingam S, Shammi C, Remington G. Treatment of clozapine-induced hypersalivation with ipratropium bromide: a randomized, double-blind, placebo-controlled crossover study. J Clin Psychiatry 2009;70:1114-9.	Toronto Nocturnal Hypersalivation Scale (TNHS)	Drug not used in UK clinical practice; Outcomes not assessed at relevant timepoints for comparison
10	Perez-Lloret S, Nano G, Katzman D, et al. A double-blind, placebo controlled, randomized, crossover pilot study of the safety and short-term antisialorrheic efficacy of multiple doses of intra-oral tropicamide films in Parkinson's disease. European journal of neurology. Volume 18, 2011:239. Lloret SP, Nano G, Carrosella A, et al. A double-blind, placebo-controlled, randomized, crossover pilot study of the safety and efficacy of multiple doses of intra-oral tropicamide films for the short-term relief of sialorrhea symptoms in Parkinson's disease patients. J Neurol Sci 2011;310:248-50. NCT. Safety and efficacy study of NH004 films for relief of sialorrhea symptoms in Parkinson's disease patients. https://clinicaltrials.gov/show/nct00761137. 2008.	Disease-specific Sialorrhoea Clinical Scale for PD (SCS-PD)	Drug not used in UK clinical practice
11	Kreinin A, Novitski D, Weizman A. Amisulpride treatment of clozapine-induced hypersalivation in schizophrenia patients: a randomized, double-blind, placebo-controlled cross-over study. Int Clin Psychopharmacol 2006;21:99-103.	Nocturnal Hypersalivation Rating Scale (NHRS)	Drug not used in UK clinical practice; Small patient numbers (n<30)
12	Kreinin A, Miodownik C, Mirkin V, et al. Double-Blind, Randomized, Placebo-Controlled Trial of Metoclopramide for Hypersalivation Associated With Clozapine. J Clin Psychopharmacol 2016;36:200-5.	Nocturnal Hypersalivation Rating Scale (NHRS)	Drug not used in UK clinical practice
13	Bai Y-M, Lin C-c, Chen J-y, et al. Therapeutic effect of pirenzepine for clozapine-induced hypersalivation: a randomized, double-blind, placebo-controlled, cross-over study. Journal of clinical psychopharmacology 2001;21:608-611.	Diameter of nocturnal saliva-wetted surface	Drug not used in UK clinical practice; Small patient numbers (n<30); Outcomes not assessed at relevant timepoints for comparison;
14	De Simone GG, Eisenchlas JH, Junin M, et al. Atropine drops for drooling: a randomized controlled trial. Palliat Med 2006;20:665-71.	Visual Analogue Scale (VAS)	Small patient numbers (n<30); Outcomes not assessed at relevant timepoints for comparison
15	Liang CS, Ho PS, Shen LJ, et al. Comparison of the efficacy and impact on cognition of glycopyrrolate and biperiden for clozapine-induced sialorrhea in	Drooling Rating Scale (DRS)	Drug combination not used in UK clinical practice; Small patient numbers (n<30)

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	schizophrenic patients: a randomized, double-blind, crossover study. Schizophr Res 2010;119:138-44.		

Abbreviations: NMA: network meta-analysis.

Beyond the different scales used, the most important secondary reasons for not using the data identified within the studies to conduct any sort of NMA include the timepoints at which each of the outcomes were assessed, as well as the patient numbers. Any NMA conducted would have required the combination of multiple timepoints, ranging from minutes to months, and the patient numbers in the vast majority of trials was n<20, which would have led to considerable uncertainty around the estimates and so would not have been informative. A summary of the timepoints assessed in each of the trials is provided below in Table 2. In addition, the majority of trials were cross-over in design, which added additional complexity to the potential analysis and finally, the overall quality of each of the studies was particularly poor.

Table 2: Summary in efficacy outcomes

Primary Outcome	Unstimulated salivary flow (g/min); saliva weight/volume (g)				Global Impression of Change (-3 to +3)					Change in drooling severity[a]						
Timepoint (weeks)	1	2	4	5	1	2	4	8	12	1	2	3	4	5	7	8
Xeomin																
SIAXI (NCT02091739)[35-39]	–	–	✓	–	–	–	✓	–	–	–	–	–	✓	–	–	–
Narayanaswami 2016 (NCT01653132)[41, 43]	–	–	✓	–	–	–	–	–	–	–	–	–	–	–	–	–
Glycopyrrolate (glycopyrronium bromide)																
Arbouw 2010[49]	–	–	–	–	–	–	–	–	–	✓[b]	✓[b]	–	✓[b]	–	–	–
Colen-De 2015[57c]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Man 2017[54]	–	–	–	–	✓	–	–	–	–	–	–	–	–	–	–	–
Scopolamine																
Brodtkorb 1988[58]	–	–	–	–	–	–	–	–	–	✓	–	–	–	–	–	–
Mato 2010[31]	–	–	–	–	–	–	–	–	–	✓	✓	–	–	–	–	–
Takeuchi 2017[56]	✓	✓	✓	✓	–	–	–	–	–	✓	✓	✓	✓	✓	–	–
Hyoscine hydrobromide																
Odachi 2017[44]	✓	–	–	–	–	–	–	–	–	✓	–	–	–	–	–	–

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Primary Outcome	Unstimulated salivary flow (g/min); saliva weight/volume (g)				Global Impression of Change (-3 to +3)					Change in drooling severity[a]						
Ipratropium bromide																
Thomsen 2007 (NCT00296946)[48]	✓	✓	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Sockalingam 2009[55]	–	–	–	–	–	✓	–	–	–	–	✓	–	–	–	–	–
Tropicamide																
Perez-Lloret 2011 (NCT00761137)[45-47]	–	–	–	–	–	–	–	–	–	✓	✓	✓	✓	–	–	–
Amisulpride																
Kreinin 2006[52]	–	–	–	–	–	–	–	–	–	✓	✓	✓	–	–	–	–
Metoclopramide																
Kreinin 2016[53]	–	–	–	–	–	–	–	–	–	✓	✓	✓	–	–	–	–
Pirenzepine																
Bai 2001[50]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	✓	✓
Atropine																
De Simone 2006[51]	–	–	–	–	–	–	–	–	–	✓	–	–	–	–	–	–
Glycopyrrolate and Biperiden																
Liang 2010[42]	–	–	–	–	–	–	–	–	–	✓	✓	✓	✓	–	–	–

Where a tick (✓) denotes that the outcome is reported at the given timepoint, and a dash (–) denotes the outcome was not reported.
[a]DSFS employed in SIAXI; various other measures employed in the different studies including NHRS, DRS and VAS scores. [b]Sialorrhoea scoring scale used to measure improvement in sialorrhoea scoring scale and responder rate was defined as an improvement by at least 30%. [c]Unable to obtain full text of Colen-De (2015)[57].
Abbreviations: g: grams; g/min: grams per minute.

In conclusion, whilst a form of NMA could have been attempted, it is still considered that the substantial heterogeneity across all of the trials detailed above would preclude the generation of robust relative effectiveness results and therefore risk drawing clinically erroneous conclusions regarding the relative clinical effectiveness of Xeomin versus the comparators that would be associated with substantial uncertainty. Moreover, the study conducted by Sridharan 2018 referred to in the ERG's question is poorly reported, and it is difficult to ascertain the exact methodology adopted. Whilst Vashista 2013 and Narayanaswami 2016 report the methods used for meta-analysis, it is not considered that the use of these approaches would have easily enabled the derivation of a relative efficacy estimate between Xeomin and glycopyrronium bromide as per the aim of the feasibility assessment.

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It was therefore considered that a more appropriate approach to test the uncertainty associated with any estimates of relative efficacy between Xeomin and the relevant comparators would be in the economic analysis, within which a conservative scenario was conducted whereby the efficacy of Xeomin plus SoC was considered equivalent to glycopyrronium bromide plus SoC. This scenario was confirmed to be overly conservative by UK clinical experts experienced in the treatment of sialorrhoea, who indicated that the efficacy of glycopyrronium bromide is by far inferior to that of Xeomin. The results of this scenario still resulted in Xeomin plus SoC dominating glycopyrronium bromide plus SoC.

A5. Please provide effectiveness data (Difference in saliva weight, Drooling Severity and Frequency Scale, response rates) and adverse event data for NCT01653132.

NCT01653132 was a randomised, placebo-controlled cross-over trial of incobotulinumtoxin A (Xeomin) 100 U versus placebo in patients between 20 and 80 years of age with clinically diagnosed Parkinson's disease and troublesome drooling, and a swallowing function >5 on the Functional Oral Intake Scale (total oral intake of multiple consistencies requiring special preparation, or better).

The primary outcome of the trial was difference in saliva weight at one month post-injection. Secondary outcomes, measured at the same timepoint, were change in Drooling Frequency and Severity Scale (DFSS) scores, proportion of subjects with >2 point improvement in DFSS scores and with >20% reduction in saliva weight. Effectiveness data for NCT01653132 are provided in Table 3 below.

Table 3: Effectiveness data for NCT01653132

Outcome	Xeomin 100 U (N=9) cross-over[a]	Placebo (N=9) cross-over[a]	Estimated difference ± SD (95% CI)
Difference in saliva weight (g), mean (SD)	-0.68 (2.40)	-0.07 (1.21)	Mean difference: -0.194 ± 0.61 (-0.71, 0.32)
Difference in Drooling Frequency and Severity Scale (DFSS) scores	-1 (1.41)	-0.67 (0.70)	Mean difference: -0.33 ± 1.41 (-1.16, 0.69)
Number of participants with response, defined as subjects with ≥2 point improvement in the DFSS scores	2	1	Risk difference: 0.33 (-0.63, 0.07)
Number of participants with response, defined as subjects with ≥20% reduction in saliva volume	3	2	Risk difference: -0.11 (-0.46, 0.28)

[a]Although the total number of patients in the trial was N=9, results are reported for all 9 patients who completed both treatment periods of the study.
Source: ClinicalTrials.gov (NCT01653132).[1]
Abbreviations: CI: confidence interval; SD: standard deviation; DFSS: Drooling Frequency and Severity Scale.

Adverse event data for NCT01653132 are presented in Table 4 below. No deaths or serious adverse events were reported.

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Table 4: Adverse event data for NCT01653132

	Xeomin 100 U (N=9) cross-over[a]		Placebo (N=9) cross-over[a]	
	Affected/at risk (%)	Number of events	Affected/at risk (%)	Number of events
Total	2/9 (22.22%)	2	0/9 (0.00%)	0
Chewing difficulty[b, c]	1/9 (11.11%)	1	0/9 (0.00%)	0
Viscous saliva[b, d]	1/9 (11.11%)	1	0/9 (0.00%)	0

Source: ClinicalTrials.gov (NCT01653132)[1]
[a]Although the total number of patients in the trial was N=9, results are reported for all 9 patients who completed both treatment periods of the study. [b]Indicates events were collected by non-systematic assessment. [c]Difficulty in chewing, a sensation of swelling inside the cheeks, a tendency to bite the inside of the cheeks and mild difficulty with motor control of the tongue, resolved in 4-6 weeks without intervention. [d]Viscous, thick saliva, mild, resolved in 4-6 weeks without intervention.

A6. Please clarify whether the phase II RCT of clostridium botulinum neurotoxin Type A (CBNT$_A$), study (NCT01565395) recruited patients with Parkinson's disease. If so, are there data for these patients?

The study NCT01565395 was withdrawn, as patients with amyotrophic lateral sclerosis (ALS) were unable to be recruited. As such, the study did not recruit patients with Parkinson's disease and therefore does not provide data for patients with Parkinson's disease.

It should be noted that NCT01565395 and NCT01653132 were originally the same study; however, due to an inability to recruit ALS patients, the ALS arm was discontinued (NCT01565395), whilst the Parkinson's disease arm went ahead (NCT01653132). Results from NCT01653132 are presented in response to Question A5 above.

A7. In Table 7 in the Appendix D the exclusion criteria states "*Sialorrhoea as an adverse event of other interventions, such as antipsychotics*". However, comparator studies of clozapine-induced hypersalivation are included (Table 8 of the Appendix). Please clarify this apparent discrepancy.

Please accept our apologies for this discrepancy. This sentence should be removed as the clinical SLR *did not* exclude studies in patients with "sialorrhoea as an adverse event of other interventions such as antipsychotics".

A8. The CSR for SIAXI states on page 4 that that an American centre had been activated. Please clarify whether this centre recruited any patients, and if so, why these results were not included in the company submission?

No patients were recruited at sites in the USA for the SIAXI trial; therefore, no results are available for patients in the USA. In the CSR for the SIAXI trial, the term 'activated' refers to clinical trial sites ready to recruit subjects, regardless of their recruitment activities, whilst the term 'active' refers to clinical trial sites that screened subjects, irrespective of whether any subjects were randomised at that site. Thus, whilst the American centre was activated, it was not active.

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A9. Please clarify whether there is expected to be a difference in drooling across time between people with a stroke, who may improve over time, and people with severe Parkinson's disease who are unlikely to improve. If there is an expected difference, please clarify why this was not accounted for in the economic model.

The anticipated EMA licence for Xeomin is broad. In line with the FDA licence received in July 2018, Xeomin is anticipated to be licensed for the treatment of adults with chronic sialorrhoea, regardless of aetiology, as the targeted mechanism of action of Xeomin is such that treatment effect is independent of the aetiology of the sialorrhoea. The anticipated Xeomin-eligible patient population is therefore likely to be highly heterogeneous. Whilst patients with stroke and patients with severe Parkinson's disease may be considered to represent two subpopulations of the overall Xeomin-eligible patient population based on underlying aetiology, this list is not exhaustive and in UK clinical practice, the overall Xeomin-eligible patient population is likely to comprise patients with a vast number of differing aetiologies. Reliable population estimates of the incidence of these conditions and the proportion of patients who may be suffering from sialorrhoea are also limited, hence it is difficult to accurately estimate the proportion of patients who might comprise each subpopulation.

The economic analysis aims to the model an average patient population reflective of UK clinical practice. Feedback from a survey of UK clinical experts conducted by Merz suggests that patients with stroke may represent ~14% of patients with sialorrhoea. As such, the proportion of these patients who may improve over time and in whom there may be expected to be a difference in drooling across time is likely to be an even smaller specific group of patients that would not comprise a sufficiently significant proportion of the population to impact on the economic model results and warrant accounting for in the model.

Furthermore, accounting for this difference in the model would require differential modelling of the natural history (in terms of change in drooling severity over time) of subgroups of patients with Parkinson's disease and with stroke. There are not enough data available from the SIAXI trial to accurately model the natural history for patients with stroke and patients with severe Parkinson's disease as two separate subpopulations: this would need to be assumed to be represented by the placebo arm, and the placebo arm provides data only up to 16 weeks and therefore does not capture any trends in changes in drooling severity over time. As such, based on the reasons listed above, possible differences in drooling over time between patients with different underlying aetiologies were not explicitly accounted for within the economic model.

A10. Clinical advice to the ERG indicates that patients with Parkinson's disease or stroke have higher rates of mortality than the average population. Please conduct a rapid review of increased mortality risk for each aetiology for values to populate the model. Further, the standardised mortality ratio (SMR) of 1.92, which was ascribed to Hobson *et al.* and used in the model appears to be 1.82 with a 95% CI of 1.55 to 2.13 in the published literature. Please correct this value in the model.

A rapid review of articles indexed in MEDLINE was conducted via PubMed using the following search terms:

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- ("standardised mortality ratio"[tiab] OR "standardized mortality ratio"[tiab] OR "mortality risk"[tiab]) AND "parkinson's disease"[tiab]
- ("standardised mortality ratio"[tiab] OR "standardized mortality ratio"[tiab] OR "mortality risk"[tiab]) AND “stroke"[tiab]

The first 50 abstracts from each search were exported and the abstracts screened for standardised mortality ratio (SMR) data. Abstracts that reported SMR values were included and top-line details of the population investigated were recorded (e.g. sample size and location, length of follow-up). A search was conducted for freely-available full texts, and if found, these were also analysed for any additional data. Otherwise, the SMR values plus any measures of uncertainty (e.g. confidence intervals) reported in the abstract alone were extracted and are presented in Table 5 below.

Table 5: Mortality risk for patients with Parkinson’s disease or stroke

Citation	Population	SMR
Parkinson’s disease		
Duarte J, Garcia Olmos LM, Mendoza A, et al. The natural history of Parkinson's disease in the province of Segovia: mortality in a longitudinal study (20-year follow-up). Acta Neurol Scand 2013;127:295-300.	273 PD patients from a single centre in Segovia, Spain	1.39 (95% CI: 1.10, 1.50) [20-year follow-up]
Hely MA, Reid WG, Adena MA, et al. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord 2008;23:837-44.	136 PD patients from multiple centres in Sydney, Australia	2.50 (95% CI: 2.00, 3.00) [3- to 20-year follow-up]
Hristova DR. Standardized mortality ratio and seasonal fluctuations of mortality in Parkinson's disease. Folia Med (Plovdiv) 2009;51:40-5.	2,274 PD patients from a single centre in Plovdiv, Bulgaria	3.60 (95% CI: 3.37, 3.95) [3-year follow-up]
Larsson V, Torisson G, Londos E. Relative survival in patients with dementia with Lewy bodies and Parkinson's disease dementia. PLoS One 2018;13:e0202044.	177 PD patients from a single centre in Malmo, Sweden	3.02 (95% CI: 2.46, 3.67) [5-year follow-up] 3.44 (95% CI: 2.92, 4.04) [10-year follow-up]
Stroke		
Aarnio K, Haapaniemi E, Melkas S, et al. Long-term mortality after first-ever and recurrent stroke in young adults. Stroke 2014;45:2670-6	970 patients with first-ever stroke from a single centre in Helsinki, Finland	Total age 15-39: 5.42 (95% CI: 3.16, 7.69) Total age 40-49: 4.44 (95% CI: 3.68, 5.21) Total age 15-49: 6.94 (95% CI: 5.84, 8.04)
De La Mata NL, Masson P, Al-Shahi Salman R, et al. Death From Stroke in End-Stage Kidney Disease. Stroke 2019;50:487-490.	60,823 patients with end stage kidney disease, from a multicentre study in Australia and New Zealand	3.40 (95% CI: 3.20, 3.60)
Meune C, Touze E, Trinquart L, et al. High risk of clinical cardiovascular events in rheumatoid arthritis: Levels of associations of myocardial infarction and stroke through a systematic review and meta-analysis. Arch Cardiovasc Dis 2010;103:253-61	Meta-analysis of cohort studies on myocardial infarction and stroke in patients with rheumatoid arthritis	Pooled SMR 1.46 (95% CI: 1.31, 1.63)

Abbreviations: SMR: standardised mortality ratio; CI: confidence interval; PD: Parkinson’s disease.

Given the range in SMR values identified in the rapid review, results of scenario analyses adopting the highest and lowest SMR values identified in the searches for both Parkinson’s disease and stroke are presented below. The results, shown in Table 6 (and conducted on the updated company base case analysis – see Section B), demonstrate that the adoption of alternative SMR values does not have a substantial effect on the base case ICER.

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Table 6: Scenario analyses

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incr. costs	Incr. QALYs	ICER (£/QALY)
Base case: no excess mortality					
Xeomin plus SoC	£6,103	3.52	-		
Glycopyrronium plus SoC	£14,966	3.34	-£8,863	0.18	Xeomin plus SoC dominant
SoC alone	£3,010	3.20	£3,093	0.32	£9,583
Scenario: highest SMR for Parkinson's disease (3.6)					
Xeomin plus SoC	£5,346	3.00	-		
Glycopyrronium plus SoC	£13,358	2.84	-£8,012	0.16	Xeomin plus SoC dominant
SoC alone	£2,558	2.71	£2,787	0.28	£9,833
Scenario: lowest SMR for Parkinson's disease (1.39)					
Xeomin plus SoC	£5,977	3.44	-		
Glycopyrronium plus SoC	£14,701	3.26	-£8,724	0.18	Xeomin plus SoC dominant
SoC alone	£2,935	3.12	£3,043	0.32	£9,620
Scenario: highest SMR for stroke (6.94)					
Xeomin plus SoC	£4,596	2.49	-		
Glycopyrronium plus SoC	£11,739	2.35	-£7,144	0.14	Xeomin plus SoC dominant
SoC alone	£2,121	2.24	£2,475	0.24	£10,158
Scenario: lowest SMR for stroke (1.46)					
Xeomin plus SoC	£5,955	3.42	-		
Glycopyrronium plus SoC	£14,654	3.24	-£8,699	0.18	Xeomin plus SoC dominant
SoC alone	£2,921	3.11	£3,034	0.32	£9,627

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care.

Please accept our apologies for the discrepancy in reporting of the SMR from Hobson *et al.,* the revised results of this scenario are presented below in Table 7 (conducted on the updated company base case analysis – see Section B).

Table 7: Revised mortality input scenarios

Intervention	Total Costs (discounted)	Total QALYs (discounted)	Incr. costs	Incr. QALYs	ICER (£/QALY)
Base case: no excess mortality					
Xeomin plus SoC	£6,103	3.52	-		
Glycopyrronium plus SoC	£14,966	3.34	-£8,863	0.18	Xeomin plus SoC dominant
SoC alone	£3,010	3.20	£3,093	0.32	£9,583
Scenario: SMR of 1.82 applied, based on Hobson *et al.* (2017)					
Xeomin plus SoC	£5,844	3.34	-		

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Glycopyrronium plus SoC	£14,419	3.17	-£8,575	0.18	Xeomin plus SoC dominant
SoC alone	£2,855	3.03	£2,990	0.31	£9,661

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care; SMR: standard mortality rate.

A11. Please provide the data used in the latent class mixed modelling approach (including the time of the assessment, the DSFS score, the EQ-5D value, patient aetiology, age and gender), and the R code used for the utility regression models explored. If available also include whether the EQ-5D value was filled in by the patient or the carer.

The following materials have been provided alongside this document:

- The data used in the latent class mixed modelling approach:
    - Patient characteristics, including aetiology, age and gender (File name: Patient Chacteristics.csv)
    - Outcome assessments, including the time of assessment, DSFS sum score and EQ-5D index score (File name: Outcome Assessments.csv)
- The R code used to explore the regression models (File name: lccm.R) and the associated R project file (File name: Merz-Submission.Rproj)

A12. Please provide parameter estimates for the coefficients and standard errors, the mean of posterior probabilities in each class, and posterior probabilities above a threshold for the utility regression model with the best statistical fit.

The model with three latent classes, class-specific mean trends, and no variable specified to inform class membership (i.e. only an intercept in the multinomial model) gave the best statistical fit. The parameter estimates for the model coefficients and standard errors are presented in Table 8. The model incorporated random effects (intercepts and slopes) to account for the correlation between repeated measures of patients. The variance-covariance matrix of the random effects is presented in Table 9. The mean of posterior probabilities in each class and posterior probabilities above a threshold are presented in Table 10 and Table 11, respectively.

Table 8: Parameter estimates for the coefficients and standard errors for the favoured LCMM

Model component	Covariate	Class	Coefficient	Standard error
Fixed effects in the class-membership model	intercept	1	[redacted]	[redacted]
		2	[redacted]	[redacted]
Fixed effects in the longitudinal model	intercept	1	[redacted]	[redacted]
		2	[redacted]	[redacted]
		3	[redacted]	[redacted]
	dsfs.factor3	1	[redacted]	[redacted]
		2	[redacted]	[redacted]
		3	[redacted]	[redacted]

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	dsfs.factor4	1	[redacted]	[redacted]
		2	[redacted]	[redacted]
		3	[redacted]	[redacted]
	dsfs.factor5	1	[redacted]	[redacted]
		2	[redacted]	[redacted]
		3	[redacted]	[redacted]
	dsfs.factor6	1	[redacted]	[redacted]
		2	[redacted]	[redacted]
		3	[redacted]	[redacted]
	dsfs.factor7	1	[redacted]	[redacted]
		2	[redacted]	[redacted]
		3	[redacted]	[redacted]
	dsfs.factor8	1	[redacted]	[redacted]
		2	[redacted]	[redacted]
		3	[redacted]	[redacted]
	dsfs.factor9	1	[redacted]	[redacted]
		2	[redacted]	[redacted]
		3	[redacted]	[redacted]
Residual standard error	-	-	[redacted]	[redacted]

Abbreviations: LCMM: latent class mixture model.

Table 9: Variance-covariance matrix of the random effects in the favoured LCMM

Random effect	Variance-covariance	
	Intercept	Week
Intercept	[redacted]	[redacted]
Week	[redacted]	[redacted]

Abbreviations: LCMM: latent class mixture model.

Table 10: Mean of posterior probabilities in each class for the favoured LCMM

Class	Probability 1	Probability 2	Probability 3
Class 1	[redacted]	[redacted]	[redacted]
Class 2	[redacted]	[redacted]	[redacted]
Class 3	[redacted]	[redacted]	[redacted]

Abbreviations: LCMM: latent class mixture model.

Table 11: Posterior probabilities above a threshold (%) for the favoured LCMM

Threshold	Class 1	Class 2	Class 3
Probability > 0.7	[redacted]	[redacted]	[redacted]
Probability > 0.8	[redacted]	[redacted]	[redacted]
Probability > 0.9	[redacted]	[redacted]	[redacted]

Probabilities 1, 2 and 3 refer to the probabilities of being in class 1, 2 and 3, respectively.
Abbreviations: LCMM: latent class mixture model.

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A13. Please provide the results on the convergence process and the goodness-of-fit data of the latent class mixed models explored.

The LCMMs explored to generate health state utility values for the economic model are shown in Table 12. The convergence process for each model, including the number of iterations, is presented in Table 13. Goodness-of-fit data for the explored models, including maximum log-likelihood estimates, Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) are presented in Table 14. The model with three latent classes, class-specific mean trends, and no variable specified to inform class membership (i.e. only an intercept in the multinomial model) (Model 4) gave the best statistical fit according to all three criteria.

Table 12: LCMMs to predict EQ-5D index scores from DSFS sum scores

Model	Linear component[a]	Number of latent classes	Class membership[b]	Class specific linear component	Random effects[c]	Number of parameters
1	~ dsfs	3	~ 1	~ 1	~ 1 + week | id	16
2	~ dsfs	2	~ 1	~ 1	~ 1 + week | id	14
3	~ dsfs	1	N/A	N/A	~ 1 + week | id	12
4	~ dsfs	3	~ 1	~ dsfs	~ 1 + week | id	30
5	~ dsfs	3	~ 1	~ dsfs	~ 1 | id	28
6	~ dsfs	3	~ age	~ 1	~ 1 + week | id	18
7	~ dsfs	3	~ aetiology	~ 1	~ 1 + week | id	20
8	~ dsfs	3	~ gender	~ 1	~ 1 + week | id	18

All models were fit to 1,385 observations pooled across all 184 patients in the SIAXI trial. The dsfs term represents the DSFS sum score as a categorical variable with eight levels; the term week represents the data collection timepoint; variable id is the patient identification number.
[a] The linear component predicts the EQ-5D index scores and is common to all classes. [b] A number of terms were explored to predict class membership in the multinomial component of the model. Aetiology is a factor with three levels (Parkinson's disease or atypical Parkinsonism, brain injury and stroke). Age was modelled as a continuous variable and gender was modelled as an indicator variable. [c] Repeated measures were accounted for through including individual specific random effects.
Abbreviations: BIC: Bayesian Information Criterion.

Table 13: Convergence process for the latent class mixed models explored

Model	Number of iterations	Criteria	Convergence		
			Parameters	Likelihood	Second derivatives
1	16	Satisfied	1.10E-06	9.30E-06	2.90E-11
2	4	Satisfied	2.20E-07	6.50E-05	1.80E-06
3	11	Satisfied	5.80E-11	4.40E-08	1.40E-15
4	34	Satisfied	8.20E-08	1.40E-07	1.10E-12
5	27	Satisfied	3.50E-05	4.50E-05	1.80E-08
6[a]	500	Maximum number of iterations reached without convergence	0.0032	0.00011	1
7	66	Satisfied	9.70E-05	7.20E-08	7.10E-07
8	113	Satisfied	9.90E-05	7.30E-08	3.80E-06

[a] Model did not converge after 500 iterations.

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Table 14: Goodness-of-fit results for the latent class mixed models explored

Model	Maximum log-likelihood	AIC	BIC
1	368.78	-705.57	-654.13
2	354.18	-680.36	-635.35
3	354.18	-684.36	-645.78
4	405.66	-751.32	-654.87
5	398.99	-741.97	-651.95
6	370.84	-705.69	-647.82
7	371.41	-702.81	-638.51
8	369.01	-702.03	-644.16

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion.

A14. Please clarify whether the discontinuation rate was dependent of DSFS group and, if so, why this was not included in the economic model.

The discontinuation rate data available from the SIAXI trial does not split out discontinuation rates according to patient DSFS score.

Overall, the main reasons for discontinuation from the Main Period (MP) of the SIAXI trial were AEs (3/11 [27.2%] in the MP) and withdrawal by the subject (8/11 [72.7%]). Whilst it is not possible to ascertain the exact reasons for subject withdrawal and whether this might have differed depending on the DSFS score of the patient, it is not expected that the rate of AEs would differ depending on the DSFS score of the patient. Lack of efficacy, which is a reason for discontinuation that might be expected to be associated with DSFS group, was reported by no patients in the MP, and only one patient in the Extension Period (EP).

As such, it was not considered appropriate to assume that discontinuation rates would be dependent on DSFS score; such an assumption was therefore not adopted within the economic model and discontinuation rates were considered independently of DSFS score.

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Section B: Clarification on cost-effectiveness data

For all analyses that result in model changes, please detail how the change was implemented in the model. Additionally, as well as providing the impact on the ICERs for the change in isolation, please perform analyses where all pertinent changes have been made simultaneously.

Based on the clarification questions received from the ERG, the company base case analysis has been updated to include the following additional assumptions:

- The last observed transition matrix for each intervention has been applied in each model cycle in the extrapolation period (Question B10)
- A continuity correction has been applied for any health state transitions that were not captured in the available data from the SIAXI trial (Question B3)
- Discontinuation rates (Question B9):
    - Discontinuation in the SoC alone arm has been set to 0
    - Patients in the active treatment arms who discontinue no longer transition to a dedicated 'Discontinued' health state, and instead are explicitly modelled across the three severity-based health states according to the transition probabilities for the SoC alone arm of the model (see Question B9 for the full description)

The deterministic base case cost-effectiveness analysis results where all of the above changes have been made simultaneously are presented in Table 15 for pairwise comparisons of Xeomin plus SoC versus glycopyrronium bromide plus SoC and SoC alone.

Table 15: Updated deterministic base case results

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incr. costs	Incr. QALYs	ICER (£/QALY)
Original base case					
Xeomin plus SoC	£5,875	3.38	-		
Glycopyrronium plus SoC	£14,571	3.12	-£8,696	0.25	Xeomin plus SoC dominant
SoC alone	£2,652	2.97	£3,223	0.41	£7,840
Updated base case					
Xeomin plus SoC	£6,103	3.52	-		
Glycopyrronium plus SoC	£14,966	3.34	-£8,863	0.18	Xeomin plus SoC dominant
SoC alone	£3,010	3.20	£3,093	0.32	£9,583

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care.

The probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA) have also been re-run and the results are presented below, where the above changes to the base case and the following changes to the sensitivity analysis inputs have been implemented simultaneously:

- Removal of the acquisition cost for Xeomin plus SoC from the sensitivity analyses (Question B4)

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- Correction of the implementation error in cells F30:G31 'SA Filter worksheet' with respect to the brackets and the 20% deviation (Question B6)

Probabilistic sensitivity analysis

The results of the PSA (1000 iterations) are presented in Table 16. The probabilistic results are similar to those estimated in the deterministic base case analysis, confirming the robustness of the base case analysis.

Table 16: Base case results (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Xeomin plus SoC	£6,141	3.49			
Glycopyrronium bromide plus SoC	£15,604	3.30	-£9,463	0.19	Xeomin plus SoC dominant
SoC alone	£2,864	3.14	£3,277	0.35	£9,482

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr.: incremental; LYG: life years gained; QALYs: quality-adjusted life years.

Scatter plots showing the incremental costs and QALYs for Xeomin plus SoC versus glycopyrronium bromide plus SoC and SoC alone are presented in Figure 1 and Figure 2 respectively. Assuming a willingness-to-pay threshold of £30,000 per QALY gained, the probability of Xeomin plus SoC being the most cost-effective treatment option is 65%. Cost-effectiveness acceptability curves for all therapies are presented in Figure 3.

Figure 1: Cost-effectiveness plane for Xeomin plus SoC versus glycopyrronium bromide plus SoC

Abbreviations: QALY: quality-adjusted life years; SoC: standard of care.

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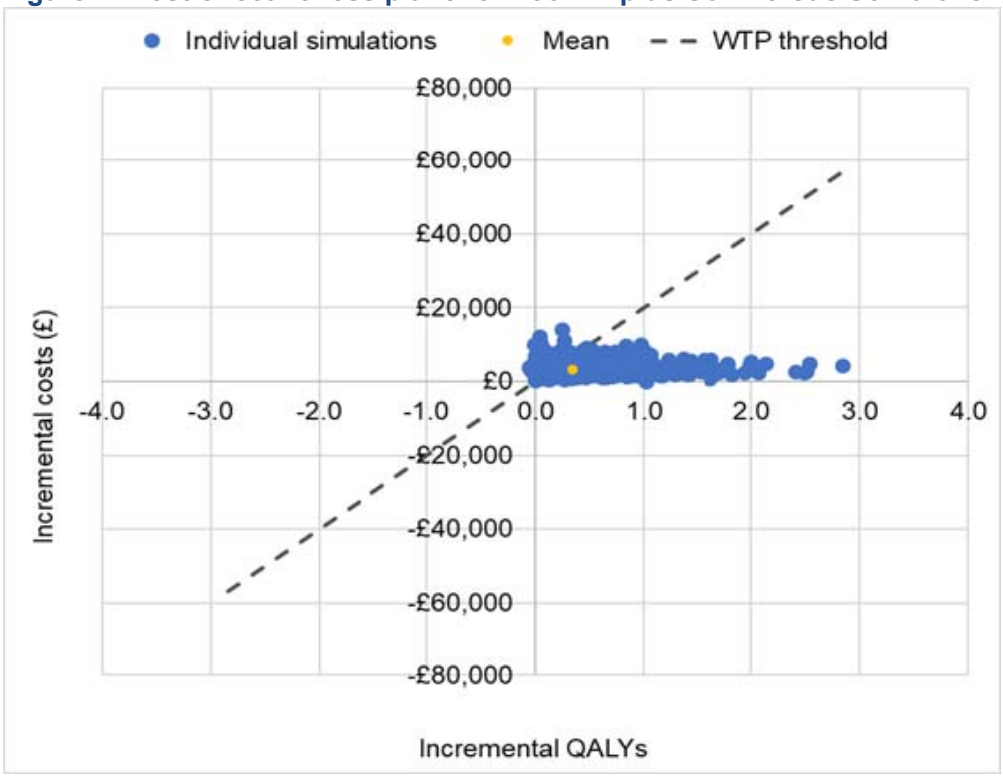
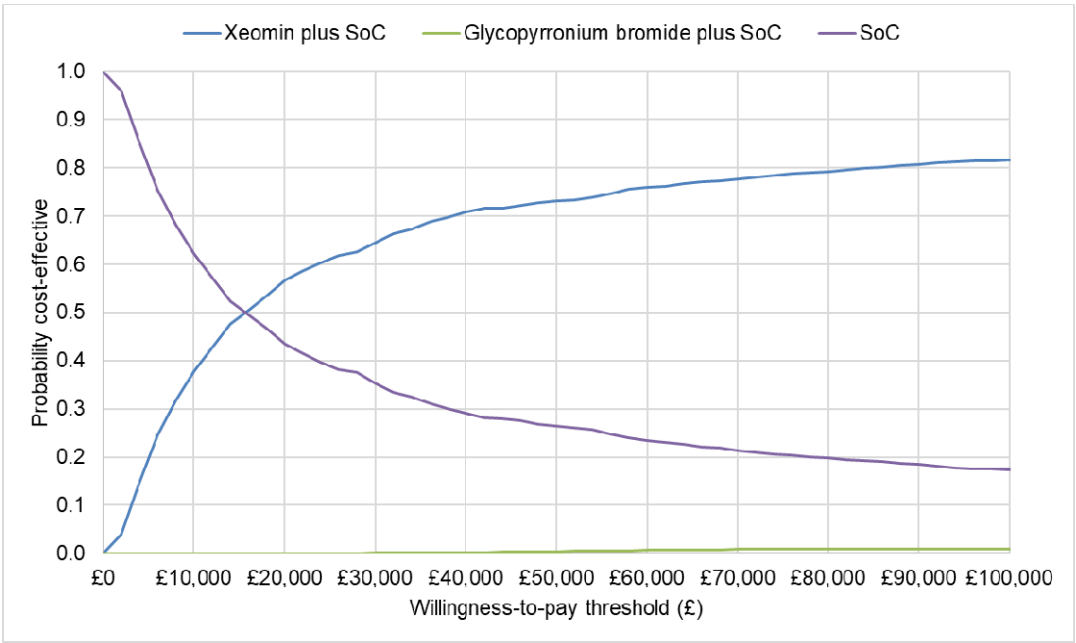
Figure 2: Cost-effectiveness plane for Xeomin plus SoC versus SoC alone



Abbreviations: QALY: quality-adjusted life years; WTP: willingness-to-pay.

Figure 3: Cost-effectiveness acceptability curve for Xeomin plus Soc versus glycopyrronium bromide plus SoC and SoC alone



Abbreviations: SoC: standard of care.

Deterministic sensitivity analysis

Tornado diagrams showing the top ten drivers of cost-effectiveness in the comparison of Xeomin plus SoC versus glycopyrronium plus SoC and SoC alone are presented in Figure 4 and Figure 5 respectively. Across these plots it can be seen that the most influential parameters included in the DSA in the comparison of Xeomin plus SoC versus glycopyrronium bromide plus SoC were

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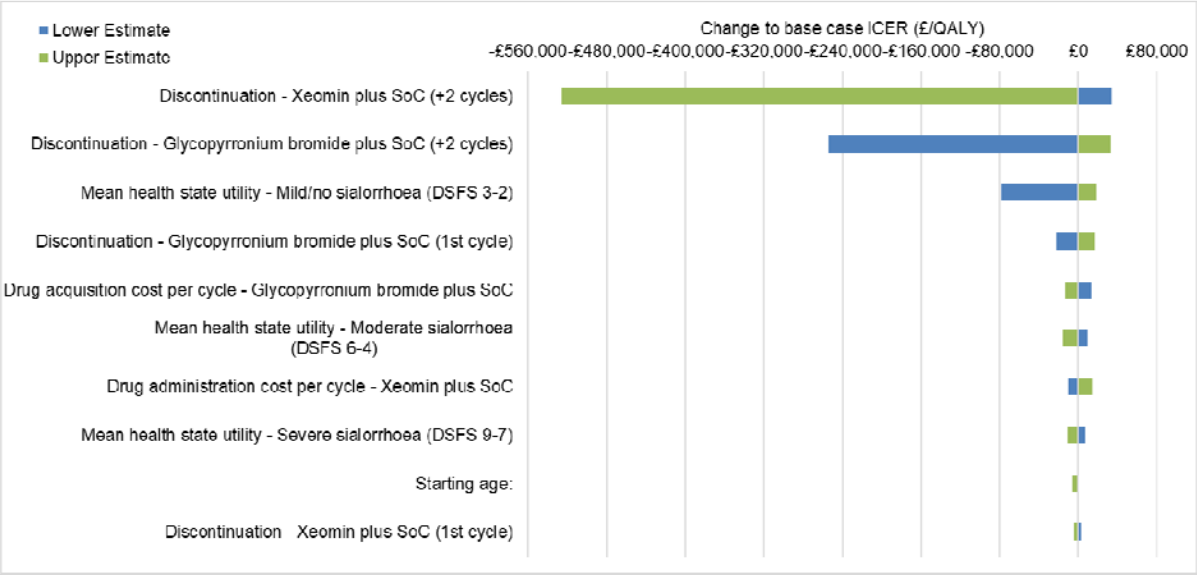
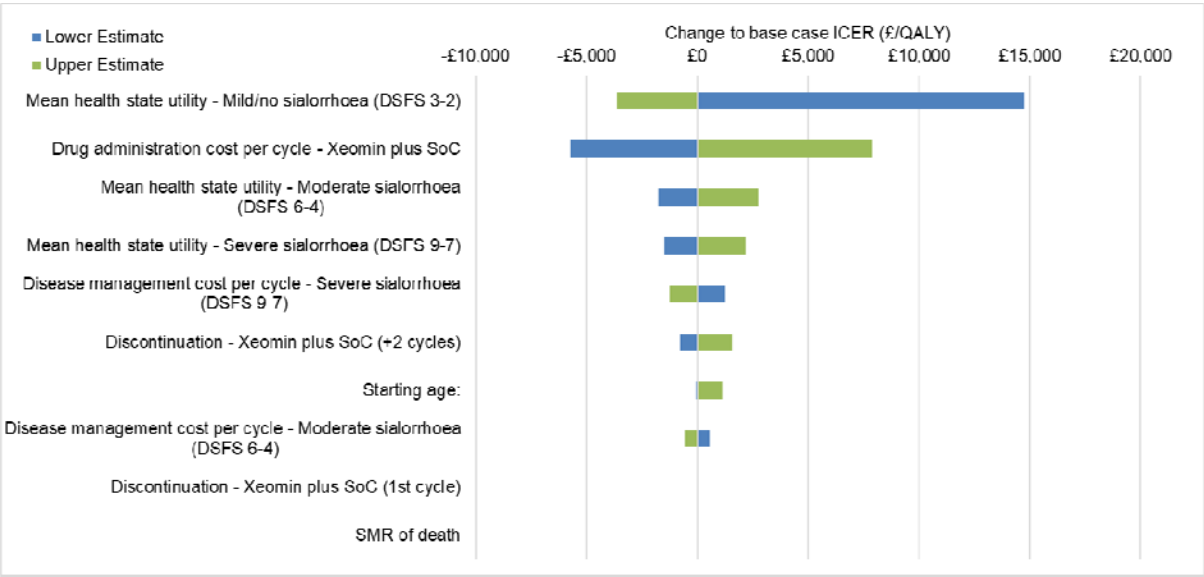
the discontinuation rates for glycopyrronium bromide plus SoC and Xeomin plus SoC. For the comparison of Xeomin plus SoC versus SoC alone, the most influential parameters in the DSA were the health state utility values for the mild/resolved and severe health states.

Figure 4: Deterministic sensitivity analysis – tornado diagram of the top ten most influential parameters versus glycopyrronium bromide plus SoC



Abbreviations: DSFS: Drooling Severity and Frequency Scale; SoC: standard of care.

Figure 5: Deterministic sensitivity analysis – tornado diagram of the top ten most influential parameters versus SoC alone



Abbreviations: DSFS: Drooling Severity and Frequency Scale; SoC: standard of care.

B1. Priority: Please clarify why ICERs were not provided broken down by drooling severity. Please provide ICERs for patients with DSFS scores 9-7, defined as 'severe' sialorrhoea in the company submission and DSFS scores 6-4, defined as 'moderate' sialorrhoea in the company submission.

Within the economic model, disease severity was categorised into three levels to ensure there were sufficient data to adequately capture transitions between health states, without

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compromising model sensitivity to adequately capture cost or treatment effects. The health states were not intended to represent subgroups for which the cost-effectiveness of Xeomin would be evaluated separately. Nonetheless, in order to transparently address the question, the results of scenarios where 100% of patients enter the model in either the "severe" or "moderate" health state, respectively, are presented in Table 17, and do not differ substantially from the base case analysis. Please note these scenarios have been conducted based on the updated company base case analysis.

Table 17: Baseline health state distribution scenarios

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incr. costs	Incr. QALYs	ICER (£/QALY)
Updated base case: 54.55% and 45.45% patients enter the model in the severe and moderate health states, respectively					
Xeomin plus SoC	£6,103	3.52	-		
Glycopyrronium plus SoC	£14,966	3.34	-£8,863	0.18	Xeomin plus SoC dominant
SoC alone	£3,010	3.20	£3,093	0.32	£9,583
Scenario: 100% of patients enter the model in the severe health state					
Xeomin plus SoC	£6,135	3.51	-		
Glycopyrronium plus SoC	£15,020	3.32	-£8,885	0.19	Xeomin plus SoC dominant
SoC alone	£3,070	3.18	£3,066	0.33	£9,162
Scenario: 100% of patients enter the model in the moderate health state					
Xeomin plus SoC	£6,064	3.54			
Glycopyrronium plus SoC	£14,900	3.37	-£8,836	0.17	Xeomin plus SoC dominant
SoC alone	£2,939	3.23	£3,125	0.31	£10,130

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care.

B2. Priority. The transition probabilities from week 36 onwards in the DSFS 9-7 health state are less favourable to $CBNT_A$ plus standard of care (SOC) rather than for SOC alone. Firstly, this appears counter-intuitive, secondly clinical input suggests that patients are unlikely to continue with $CBNT_A$ and clinicians / funders unlikely to persist with this treatment, if it were perceived not to be beneficial. Please perform an analysis where patients discontinue $CBNT_A$ if they are in the DSFS 9-7 health state after 20 weeks (where the efficacies, in the severe drooling state, of $CBNT_A$ plus SOC and SOC are similar)

Data from the Xeomin 100U and placebo arms of the SIAXI trial were utilised to produce the transition matrices for the Xeomin plus SoC and SoC alone arms of the model, respectively. As per Question B10, in the updated company base case analysis, the last observed transition probability matrix in each arm has been applied to every cycle in the extrapolation period to estimate health state distribution. Data were available for Xeomin plus SoC for four model cycles, whereas data for the SoC alone arm were only available for one model cycle. Therefore, the transition probabilities for the severe health state (DSFS: 9–7) from week 36 onwards (i.e. applied to transitions from the fourth model cycle onwards) for the Xeomin plus SoC arm (based on data from the SIAXI trial) appear to be less favourable than for SoC alone (extrapolated from

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the first model cycle), as shown in Table 18. Given that the probabilities in Table 18 propagate through the model time horizon, the implication of this is that patients in the severe health state receiving Xeomin plus SoC have a lower probability of improving in the long term than those receiving SoC alone, which appears counter-intuitive.

Table 18: Transition probabilities

Transitions[a]	Model arm	Initial health state	Transition probability to subsequent health state (%)[b]		
			9-7	6-4	3-2
Applied from cycle 4 onwards	Xeomin plus SoC	9-7	[redacted]	[redacted]	[redacted]
	SoC alone		[redacted]	[redacted]	[redacted]

[a] As per Question B10, the last observed transition probability matrix in each arm has now been applied to every cycle in the extrapolation period to estimate the health state distribution.
[b] Please note that these are the transition probabilities observed without applying the continuity correction discussed in Question B3.
Abbreviations: SoC: standard of care.

Firstly, it is important to note that the transition probabilities in both the Xeomin plus SoC and SoC alone arms of the model are subject to uncertainty. In the Xeomin plus SoC arm, data for very few patients (n=5) informed the transition probabilities applied from the fourth model cycle for the severe health state. In the SoC alone arm, data from the SIAXI trial were only available for one model cycle, so one set of transition probabilities were applied to all transitions in the model, requiring an assumption that the efficacy observed in the first 16 weeks holds at later timepoints. The counter-intuitive transition probabilities presented in Table 18 may therefore simply represent a statistical artefact inherent in the uncertainty, and potentially not a robust basis for informing clinical decision-making regarding continued treatment in practice.

Additionally, it is also worth noting the potential clinical implications of stopping treatment with Xeomin in patients who have severe sialorrhoea after a given timepoint. Since the severity-based health states in the model span multiple DSFS states, a lack of transition out of this health state does not necessarily equate to a lack of treatment benefit. Improvements in DSFS scores can be observed within health states. In fact, of the patients informing the transition probabilities in Table 18 for Xeomin plus SoC, an improvement in DSFS score was observed for [redacted]% ([redacted]) patients. However, most of these improvements in DSFS score did not result in a change in health state assignment. In contrast, of the patients informing the transition probabilities for SoC alone, an improvement in DSFS score was only observed for [redacted]% ([redacted]) patients, but a higher proportion of these improvements in DSFS scores resulted in a change in health state assignment. As such, similarity between the transition probabilities presented in Table 18 does not necessarily indicate that patients who are still in the severe health state in that particular model cycle are no longer deriving any clinical benefit from treatment with Xeomin plus SoC.

Whilst it is acknowledged that clinicians are unlikely to persist with treatment if it were perceived not to be beneficial, applying a stopping rule for patients who are in the severe health state at an arbitrary time point (i.e. where the transition probabilities are similar for both Xeomin plus SoC and SoC alone) is not considered reflective of how decisions regarding treatment discontinuation would be made in UK clinical practice. These decisions would be based on the length of time a patient had gone without responding to treatment, not the probability of moving to a less severe health state in the subsequent 16 weeks. As such, a stopping rule has not been included within the updated company base case analysis.

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However, in order to transparently address the question, scenarios including a stopping rule where patients who are in the severe health state discontinue Xeomin plus SoC at cycle 2, 3 or 4 have been conducted and the results of these scenario analyses are presented in Table 19. Please note that these scenarios incorporate all of the additional assumptions included in the updated company base case analysis, including the changes to discontinuation discussed in Question B9 and the continuity correction discussed in Question B3. As such, the transition probabilities from week 36 onwards are no longer less favourable to Xeomin plus SoC compared to SOC alone.

Table 19: Application of stopping rule

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incr. costs	Incr. QALYs	ICER (£/QALY)
Updated base case: no stopping rule					
Xeomin plus SoC	£6,103	3.52	-		
Glycopyrronium plus SoC	£14,966	3.34	-£8,863	0.18	Xeomin plus SoC dominant
SoC alone	£3,010	3.20	£3,093	0.32	£9,583
Change to model: patients in the severe health state at cycle 2 discontinue active treatment					
Xeomin plus SoC	£5,860	3.50	-		
Glycopyrronium plus SoC	£13,562	3.33	-£7,702	0.17	Xeomin plus SoC dominant
SoC alone	£3,010	3.20	£2,850	0.30	£9,594
Change to model: patients in the severe health state at cycle 3 discontinue active treatment					
Xeomin plus SoC	£5,911	3.50			
Glycopyrronium plus SoC	£13,928	3.33	-£8,016	0.17	Xeomin plus SoC dominant
SoC alone	£3,010	3.20	£2,901	0.30	£9,572
Change to model: patients in the severe health state at cycle 4 discontinue active treatment					
Xeomin plus SoC	£5,893	3.50			
Glycopyrronium plus SoC	£13,961	3.33	-£8,068	0.17	Xeomin plus SoC dominant
SoC alone	£3,010	3.20	£2,883	0.30	£9,568

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care.

B3. Priority. The transition probabilities used in the model imply that some transitions are impossible, for instance no-one can move from the DSFS 6-4 health state to the DSFS 3-2 health state when receiving SOC, and that no-one can move from the DSFS 6-4 health state to the DFS 9-7 health state in the third cycle when receiving CBNT$_A$ plus SOC. Please clarify why a continuity correction was not applied, such as dividing an additional unit equally across all health states. Please perform an analysis using such a method.

The company base case analysis has now been updated to include a continuity correction for all relevant transitions and the results of the updated company base case analysis are presented in

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Table 20. In all model cycles, for any given starting health state where the probability of transitioning to another health state was zero, a continuity correction integer of 1 was applied across the suite of transitions.

The results for this change to the model in isolation compared with the original base case analysis are presented below in Table 20.

Table 20: Application of a continuity correction

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incr. costs	Incr. QALYs	ICER (£/QALY)
Original base case: no continuity correction					
Xeomin plus SoC	£5,875	3.38	-		
Glycopyrronium plus SoC	£14,571	3.12	-£8,696	0.25	Xeomin plus SoC dominant
SoC alone	£2,652	2.97	£3,223	0.41	£7,840
Change to model: application of continuity correction					
Xeomin plus SoC	£5,893	3.37	-		
Glycopyrronium plus SoC	£14,566	3.13	-£8,673	0.24	Xeomin plus SoC dominant
SoC alone	£2,615	2.98	£3,278	0.39	£8,405

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care.

B4. Please clarify why the sensitivity analysis included an estimation of an uncertainty of acquisition cost for CBNT$_A$. Please perform analyses with this cost fixed.

Thank you for highlighting this. This was an oversight, which has now been corrected in the sensitivity analysis: no uncertainty associated with acquisition costs for Xeomin plus SoC has been included in the sensitivity analyses. Both the DSA and PSA have now been re-run, and results of these analyses are presented above.

B5. Please clarify how the uncertainty related to values of transition probabilities and baseline health state distribution proportions was handled in the probabilistic sensitivity analysis (PSA). Please state in detail how the stated probability distribution (Dirichlet (from Gamma)) was used to obtain the parameter values for the PSA. Please clarify also why this uncertainty was not included in the deterministic sensitivity analysis (DSA), and perform a DSA where these uncertainties are included.

Transition probabilities were sampled from a Dirichlet distribution for the PSA, using the standard approach of first sampling from independent Gamma(x,1) distributions, where the shape parameter x was taken equal to the number of observed transitions in the IPD in each case. A normalised sum of each group of three Gamma random variables was then taken to determine the transition probabilities for each iteration of the PSA.[2]

It was not considered appropriate to include the transition probabilities within the DSA, since the DSA is a one-way sensitivity analysis and the transition probabilities are not independent variables.

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For completeness, the uncertainty associated with the transition probabilities has been explored deterministically by manually adjusting the most influential transition probabilities by ±20% (with a lower bound of 0.01). The other transition probabilities were adjusted proportionally, so that the suite of transition probabilities summed to 1. The results are presented in Table 21 below.

Table 21: Scenarios to test the uncertainty in transition probabilities

Model arm	Matrix affected (transition affected)	Transition probability varied by +/- 20%	ICER (£/QALY) versus glycopyrronium bromide plus SoC		ICER (£/QALY) versus SoC	
			Lower	Upper	Lower	Upper
Xeomin plus SoC	Baseline to week 4	9-7 to 6-4	Xeomin plus SoC dominant	Xeomin plus SoC dominant	£9,610	£9,555
	Baseline to week 4	6-4 to 6-4[a]	Xeomin plus SoC dominant	Xeomin plus SoC dominant	£9,616	£9,566
	Week 4 to week 20	6-4 to 6-4	Xeomin plus SoC dominant	Xeomin plus SoC dominant	£9,718	£9,543
	Week 20 to week 36	6-4 to 6-4	Xeomin plus SoC dominant	Xeomin plus SoC dominant	£9,681	£9,709
	Week 36 to week 52	6-4 to 6-4	Xeomin plus SoC dominant	Xeomin plus SoC dominant	£9,649	£9,563
	Extrapolated	6-4 to 6-4	Xeomin plus SoC dominant	Xeomin plus SoC dominant	£9,973	£9,443
	Extrapolated	3-2 to 3-2	Xeomin plus SoC dominant	Xeomin plus SoC dominant	£13,216	£6,888
SoC	Baseline to week 4	9-7 to 9-7	Xeomin plus SoC dominant	Xeomin plus SoC dominant	£9,826	£9,366
	Baseline to week 4	6-4 to 6-4	Xeomin plus SoC dominant	Xeomin plus SoC dominant	£9,518	£9,712
	Extrapolated	9-7 to 9-7	Xeomin plus SoC dominant	Xeomin plus SoC dominant	£11,515	£7,572
	Extrapolated	6-4 to 6-4	Xeomin plus SoC dominant	Xeomin plus SoC dominant	£8,807	£13,670

[a] To ensure that the selected transition probability did not exceed 1, the transition probability was varied by +/- 10%

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care.

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B6. There appears to be implementation errors in cells F30:G31 of the 'SA Filter worksheet' with respect to the brackets and the 20% deviation. Please amend these apparent errors.

Thank you for highlighting this implementation error; this has now been corrected. The PSA has now been re-run, and results of this analysis are presented above.

B7. The ERG believes that an arbitrary 20% change is not appropriate for uncertainty in NHS reference costs. Earlier editions could be used to quantify the ratio between the mean and its standard error which could be assumed generalisable to the latest values. Please provide an analysis where this approach is used.

The use of an arbitrary change to represent the uncertainty in NHS reference costs has been included in a variety of previous NICE appraisals (e.g. TA490).[3] However, the standard errors for NHS reference costs have now been derived from the lower/upper quartiles reported for the NHS reference costs across the last 4 years and both the DSA and PSA have now been re-run; results of these analyses are presented above.

B8. It is stated in the Model Structure section (page 70) that "for patients that discontinued treatment, their sialorrhoea severity was assumed to revert to the mean severity observed at baseline". Please clarify why a similar approach was not followed for measuring health-state associated costs for patients who discontinue treatment. Please perform an analysis with this change implemented.

A scenario has been conducted where health state costs for patients who discontinue treatment have been calculated as a weighted average of the health state costs for the severe and moderate health states according to the baseline health state distribution. The results for this change to the model in isolation compared with the original base case analysis are presented in Table 22.

Table 22: Adjustment of costs distribution in discontinued health state

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incr. costs	Incr. QALYs	ICER (£/QALY)
Original base case					
Xeomin plus SoC	£5,875	3.38	-		
Glycopyrronium plus SoC	£14,571	3.12	-£8,696	0.25	Xeomin plus SoC dominant
SoC alone	£2,652	2.97	£3,223	0.41	£7,840
Change to model: Adjustment of costs distribution in discontinued health state					
Xeomin plus SoC	£6,461	3.38			
Glycopyrronium plus SoC	£15,484	3.12	-£9,023	0.25	Xeomin plus SoC dominant
SoC alone	£3,567	2.97	£2,893	0.41	£7,038

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care.

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Due to subsequent updates to the modelling of discontinuation, please note that this approach to estimating health state costs for patients who discontinue was not included in the updated base case. As per the response to Question B9, in the updated company base case analysis, patients who discontinue active treatment no longer transition to a dedicated 'Discontinued' health state but are instead explicitly modelled across the three severity-based health states according to the transition probabilities for the SoC alone arm of the model. These patients therefore accrue no further treatment acquisition or administration costs but continue to accrue health state costs and health-related utility according to their severity-based health state occupancy.

B9. The ERG believes that the approach used for patients who discontinue treatment would be biased towards treatments with a small percentage of discontinuation. The ERG believes that the following approach would be less biased:

[redacted] **Note that these numbers would change if the transition probabilities are altered in response to clarification question B3. Please perform an analysis using the method suggested by the ERG.**

Please note that before methods to model discontinuation were explored, the model was updated as per Question B10 and Question B3, so that the last observed transition matrix for each intervention was applied in each model cycle in the extrapolation period and the continuity correction was applied.

The new company base case analysis has been updated such that no patients in the SoC alone arm of the model discontinue. Transition probabilities for the SoC alone arm of the model have then been used to model patients who discontinue treatment in the Xeomin plus SoC and glycopyrronium bromide plus SoC arms of the model, since these patients would continue to receive SoC alone in clinical practice. Two approaches were considered to model discontinuation from the active treatment arms:

1) Patients in the active treatment arms who discontinue transition to a dedicated 'Discontinued' health state, as per the model structure in the original base case analysis, where the health state utility values and health state costs represent weighted averages of the utility values and health state costs of the severity-based health states according to the health state distribution of a steady state of a closed population using the transition probabilities for SoC ([redacted]% severe; [redacted]% moderate; [redacted]% mild).

2) Patients in the active treatment arms who discontinue treatment do not transition to a dedicated 'Discontinued' health state, but instead continue to be explicitly modelled across the three severity-based health states. Following discontinuation, patients are modelled in an identical fashion to those in the SoC alone arm of the model: transitions between health states are based on transition probabilities for the SoC alone arm of the model, patients no longer accrue treatment acquisition or administration costs, and health state costs and health-related utility are accrued according to severity-based health state occupancy.

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Scenarios were conducted where discontinuation was modelled using both of the two approaches described. The results for these changes to the model (in addition to the updates to extrapolation and continuity correction discussed in Questions B10 and B3, respectively) compared to the original base case analysis are presented in Table 23.

Table 23: Discontinuation changes

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incr. costs	Incr. QALYs	ICER (£/QALY)
Original base case					
Xeomin plus SoC	£5,875	3.38	-		
Glycopyrronium plus SoC	£14,571	3.12	-£8,696	0.25	Xeomin plus SoC dominant
SoC alone	£2,652	2.97	£3,223	0.41	£7,840
Scenario: Approach (1)					
Xeomin plus SoC	£6,112	3.52			
Glycopyrronium plus SoC	£14,961	3.34	-£8,849	0.18	Xeomin plus SoC dominant
SoC alone	£3,010	3.20	£3,102	0.32	£9,721
Scenario: Approach (2) (i.e. the updated base case)					
Xeomin plus SoC	£6,103	3.52	-		
Glycopyrronium plus SoC	£14,966	3.34	-£8,863	0.18	Xeomin plus SoC dominant
SoC alone	£3,010	3.20	£3,093	0.32	£9,583

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care.

Since the ICERs produced were very similar, the second approach was considered to be more appropriate given the lack of a requirement for a simplifying assumption (i.e. patients are no longer modelled to transition between health states). This approach was also considered to more accurately represent the trajectory of patients who discontinue active treatment in clinical practice. As such, this approach was included in the updated company base case analysis.

B10. Priority: After week 52 the model assumes that patients who neither discontinue or die, remain in the same DSFS state. Please clarify why this approach was believed preferable to assuming that the last observed matrix for each intervention would be applicable to each cycle. Perform an analysis where the last observed matrix was used in the extrapolation period.

Please note that question B10 is related to questions B2 and B9 – please consider this in your answers to those questions.

On reflection, we agree that the continued potential to transition between severity-based health states in the post-trial period may be more clinically realistic, so the updated company base case analysis has now been updated where the last observed transition matrix for each intervention has been applied in each model cycle in the extrapolation period. The results for this change in isolation compared with the original base case analysis are presented in

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Table 24.

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Table 24: Transition matrix extrapolation

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incr. costs	Incr. QALYs	ICER (£/QALY)
Original base case					
Xeomin plus SoC	£5,875	3.38	-		
Glycopyrronium plus SoC	£14,571	3.12	-£8,696	0.25	Xeomin plus SoC dominant
SoC alone	£2,652	2.97	£3,223	0.41	£7,840
Change to model: transition matrix extrapolation					
Xeomin plus SoC	£5,732	3.43			
Glycopyrronium plus SoC	£14,487	3.16	-£8,754	0.27	Xeomin plus SoC dominant
SoC alone	£2,584	3.00	£3,148	0.43	£7,244

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SoC: standard of care.

Section C: Textual clarification and additional points

C1. In Table 58 of the company's submission, the mean utility values for the severe, moderate and mild/no sialorrhoea health state [redacted], respectively. These did not match the values used in the economic model. Please clarify this apparent discrepancy.

Apologies for this discrepancy. The values used in the economic model are correct; the mean utility values for the severe, moderate and mild/no sialorrhoea health states should be 0.3008, 0.4283 and 0.5346, respectively.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Clostridium botulinum neurotoxin type A for treating chronic sialorrhoea [ID1150]

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.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	Parkinson's UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Parkinson's UK has around 35,000 members. We provide support and advice to people with Parkinson's and their families and friends through our network of local advisers and 450 local support groups. We want everyone to get the best health and social care, so we bring professionals together to drive improvements that enable people to live life to the full. We also inspire and support the international research community to develop life-changing treatments, faster. We are funded by donations.

4b. 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?	Through consultation with several speech and language therapists who are part of the UK Parkinson's Excellence Network and people with Parkinson's and carers.
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?	We estimate there are 145,000 people living in the UK with Parkinson's. By 2025 we expect the number of people with Parkinson's will rise by nearly a fifth to 168,582 and by 2065 it is expected to have doubled, due to an ageing population. While the majority of people develop Parkinson's symptoms after the age of 65, thousands of working age people are also affected (Parkinson's UK, 2018 - https://www.parkinsons.org.uk/news/parkinsons-diagnoses-set-increase-fifth-2025 accessed 16 May 2019). Parkinson's is a progressive, fluctuating neurological condition that affects all aspects of daily living including talking, swallowing and writing. Every person's symptoms are different. People with Parkinson's often find it hard to move freely. There are also other issues such as pain, depression, anxiety, dementia, freezing, hallucinations, and continence problems. The severity of symptoms can fluctuate from day to day and people can experience rapid changes in functionality over the course of the day. There is no cure for the condition, but medication can help people manage their symptoms. However, these regimes can be complex and over time medication can become less effective at controlling symptoms. Recent research undertaken by Parkinson's UK showed that 87% of people with Parkinson's have faced harassment and discrimination and over half are avoiding or cancelling social situations due to negative experiences. That figure rises to 99% among people aged 40-50, highlighting the additional challenge of being diagnosed with Parkinson's when you're younger. (Parkinson's UK, 2019 - https://www.parkinsons.org.uk/news/world-parkinsons-day-survey-reveals-harassment-faced-people-parkinsons accessed 13 May 2019). This is relevant to this technology as it helps people who experience excessive drooling of saliva or problems eating due to a lack of control of facial muscles. This can be a troubling symptom of the condition that people have shared has stopped them going out due to the way they're treated by the public who don't understand the condition.

	Carers of people with Parkinson's often report carer stress is a major factor. Research indicates that the quality of life and wellbeing of carers of people with Parkinson's decreases as the condition progresses and the longer they have been caring for them (Hand et al, 2013 - https://onlinelibrary.wiley.com/doi/abs/10.1111/ggi.12204 accessed 13 May 2019). Therefore, greater formal care input including interventions to reduce drooling of saliva and help people swallow safely may enable people to live at home longer and also may reduce care home admissions and avoid some unplanned hospital admissions. Also, caregivers and families of people with Parkinson's face accentuated financial distress, in addition to the physical and psychological changes of the condition, which could include excessive drooling of saliva or problems with swallowing. Research reveals that a household where someone has Parkinson's in the UK is on average £16,582 per year worse off (Parkinson's UK, 2017 - https://www.parkinsons.org.uk/news/whats-cost-living-parkinsons accessed 13 May 2019).
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The patient reported experience measure of the UK Parkinson's Audit 2017 (2017 UK Parkinson's Audit, reference report - https://www.parkinsons.org.uk/sites/default/files/2018-06/Reference%20Report_2017.pdf accessed 13 May 2019) shows that: • 70% of elderly care consultants and 60% of neurologists had completed a swallow assessment in the past year with their patients • Around 80% of elderly care consultants and neurologists involved speech and language therapists in their multidisciplinary teams • 89% of people responding rate the service they receive from their elderly care consultant or neurologist as excellent, good or fair. • 32% of people with Parkinson's across the UK that responded have been able to access speech and language therapy while 3% have tried and failed to access it. • 22% of people with Parkinson's who responded were able to access speech and language therapy between scheduled reviews, while 6% couldn't access any service. • Almost 25% of respondents think their speech and language therapy service is either excellent or good.
8. Is there an unmet need for patients with this condition?	People with Parkinson's can access Clostridium botulinum neurotoxin type A in a variety of ways. Either through their consultant, a referral from their Parkinson's nurse or through a referral by a speech and language therapist.

	Speech and language therapists, we consulted for this response shared that access to this technology can be variable across England and Wales, therefore we believe there is an unmet need for this technology.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	As Parkinson's impacts everyone differently clinicians we consulted estimated around 50% of their patients using the technology report it works well, 30% think it is good but isn't completely effective and between 15-20% say it makes no difference. The technology is most effective at managing thin watery saliva.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	It can sometimes affect swallowing and make people more prone to choking on more complex food textures. Clinicians who shared this concern noted they took time to explain this to patients. They share information on foods to avoid and strategies to deal with any choking incidents to mitigate this risk.
Patient population	
11. Are there any groups of patients who might benefit from the technology than others? If so, please describe them and explain why.	People who experience excessive drooling of saliva as Clostridium botulinum neurotoxin type A, deactivates the saliva glands, typically either the submandibular or parotid or both. This technology is typically used for people with Parkinson's at the advanced stage of the condition as other treatment interventions are utilised by clinicians first. Professionals who shared their experience with us noted that around 90% of people with Atypical Parkinson's (MSA/PSP) often need it.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Age**: The condition predominantly impacts people over 65 years old, but thousands of working age people are also living with the condition. **Physical disabilities**: Parkinson's is a movement related disorder. The most common symptoms of the condition are slowness of movement, rigidity and stiffness. People tend to have saliva management issues because of changes to their posture and reduced lip seal. **Communication difficulties**: People with Parkinson's often have problems with the quality and volume of their voice, which can reduce their ability to communicate clearly. Speech and language therapists are a key part of a multidisciplinary team that supports people with the condition to live well. **Mental health problems**: People with Parkinson's often report anxiety or depression as the most distressing aspect of their condition. Studies have found people that 31% of people living with the condition experience anxiety (Broen MPG et al (2016) 'Prevalence of anxiety in Parkinson's disease: a systematic review and metaanalysis' *Movement Disorders;* 31: 1125–1133) and 40% experience depression (Aarsland D et al (2012) 'Depression in Parkinson's disease – epidemiology, mechanisms and management' *Nature Reviews Neurology;* 8: 35–47). These figures are higher than the one in six experiencing common mental health problems in the general population.
Other issues	
13. Are there any other issues that you would like the committee to consider?	N/A

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • While this technology can be prescribed by consultants, nurses and speech and language therapists we believe due to variable services access to this technology is also variable and there is an unmet need. • This treatment can be useful for the Parkinson's population, usually those with more advanced Parkinson's and when other interventions have been utilised. • There should be clear guidance on the appropriate use of this technology and professionals supervising the use should ensure suitable advice is provided to people with Parkinson's and carers to ensure the treatment is effectively administered and any issues with choking are minimised.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Clostridium botulinum neurotoxin type A for treating chronic sialorrhoea [ID1150]

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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Association of British Neurologists**
3. Job title or position	[redacted]

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 this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists is a non for profit membership association for Neurologists whose mission is to improve the health and well-being of people with neurological disorders by advancing the knowledge and practice of neurology in the British Isles.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**n/a**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reduce excess saliva production which is a feature of neurological disorders including Parkinson's and similar disorders, and motor neurone disease.

7. 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.)	A reduction in drooling of saliva, that reduces unpleasant dribbling onto clothes, or reduces irritation at the corners of the mouth
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	There are limited treatment options. Anticholinergic therapy is the traditional treatment but causes cognitive and neuropsychiatric problems, particularly when there is cognitive impairment (elderly, people with Parkinson's)
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	No
• Is the pathway of care well defined? Does it	It is included in NICE guidelines

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?	Additional option of more targeted treatment without cognitive side effects
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	Toxin injections are provided at other sites for other indications in most movement disorder services eg. neck and face for dystonia. This indication is different and the techniques for injection are a new skill.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics in secondary care.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training of staff in injection techniques.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or	No

less effective (or appropriate) than the general population?	
The use of the technology	
13. 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 acceptability or ease of use or additional tests or monitoring needed.)	More difficult in requiring injections.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology?	Lack of benefit from toxin injections in other indications is generally assessed (informally) by adjusting doses and sites over 3 consecutive treatment cycles and deciding if benefit is evident, and stopping if this is ineffective (this is for identifying primary non-responsiveness). However, some patients become immune to

Do these include any additional testing?	toxin, and there is an option to try Type B toxin, and then similarly decide after 2-3 cycles of treatment if there is efficacy. Treatment is also stopped if signifcant side effects develop.
15. 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?	No
16. 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?	No
• Is the technology a 'step-change' in the	No

management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	Yes, the available treatments lack efficacy and have systemic side effects
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Swallowing difficulties and excessive dryness of the mouth can arise from too high a dose. These adverse effects are self-limiting, but in rare cases can be troublesome.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important	Saliva flow rate and overall efficiacy regarding change, yes.

outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. How do data on real-world experience compare with the trial data?	No data
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	NA

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Targeted treatment
- Avoids systemic side effects
- Fits with movement disorder services
- Not required in most patients
-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Clostridium botulinum neurotoxin type A for treating chronic sialorrhoea [ID1150]

Thank you for agreeing to give us 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.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor K Ray-Chaudhuri (Ray Chaudhuri)**
2. Name of organisation	**King's College Hospital, NHS Foundation Trust, Denmark Hill, London SE5 9RS**
3. Job title or position	**Professor of Movement Disorders and Medical Director of the National Parkinson Foundation International Centre of Excellence**
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 this condition? ☒ a specialist in the clinical evidence base for this condition 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 didn't submit one, I don't 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
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Sialorrhoea is the anterior (drooling from the mouth) or posterior (compromised swallowing of saliva) loss of control of saliva. Most commonly, sialorrhoea is due to either dysfunction in control of the orofacial musculature, dysphagia, or, less commonly, hypersalivation. Sialorrhoea can have a significant negative impact on both quality of life and patient health across a wide variety of neurological disorders, regardless of underlying aetiology. In particular, sialorrhoea occurs in all stages of Parkinson's Disease (PD). The aim of the use of clostridium botulinum toxin serotype A (Xeomin®) is to reduce production of saliva by focal injection into the parotid and sub-mandibular salivary glands thus allowing for greater control of salivary secretions in patients with compromised salivary control. This, in turn, will reduce the deleterious effects of poor salivary control.
8. 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.)	Specific measures exist for the quantification of salivary control and the production of saliva. However, quantitative measures of saliva/drooling can be difficult to administer and invasive. In the time-constrained clinical environment subjective, qualitative measures are preferred. Significant change in the subjective Drooling Severity and Frequency Score (DSFS) has been shown (Rashnoo *et al.* 2015) to correlate well with objective measures of drooling of saliva. Significant changes from a patient's initial/baseline state, as measured by the DSFS or the physician's/patient's Global Impression of Change Scale, correlate well with observed changes in clinic. Reports by patients that their sialorrhoea has improved, and as such reduced their social isolation for example, follow the change in these measures well.

9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, significantly so. There is a wide variation in treatment and a comparative lack of high quality evidence and advice regarding the treatment of sialorrhoea.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Current treatment varies across disease severity
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NG-42 (Motor Neuron Disease) and NG-71 (Parkinson's Disease) are the principle national guidelines used in neurology. As all treatments for chronic sialorrhoea in adults were off-licence until the granting of a licence to Xeomin this year, practice has been heterogeneous and wider guidance has been somewhat lacking.
• 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.)	There is no well-defined pathway of care for management of sialorrhoes worldwide in PD. A special case as the problems may occur from the *de novo* stage of PD to very late palliative stage. Overall prevalence in PD is thought to be 35% in PD across la stages versus a control population (p = 0.0004) and figures can rise to 80%. In spite of this, the problem is often not declared to clinicians (even though it causes social isolation). 45.5% of patients did not report bothersome sialorrhoea in an international study, and drooling of saliva is rated as the 3rd most bothersome problem for PD based on a study in 173 patients across London who were asked rate the top 10 bothersome symptoms affecting their lives. The NICE guidelines specifies management of drooling with non-pharmacological management initially, followed by glycopyrronium bromide as the first line pharmacological therapy, and, if glycopyrronium bromide is ineffective, not tolerated, or contraindicated, then refer to specialist services for injection of clostridium botulinum toxin serotype A. However, the evidence based guidelines from the Movement Disorders Society (followed worldwide and published in 2019) states that clostridium botulinum toxin serotype A is "clinically useful", whereas glycopyrronium bromide is only "possibly useful" for the short term management of sialorrhoea. The SIAXI trial, and significant clinical experience with Xeomin's use to treat sialorrhoea, supports its use within its licenced indication long term, and, where appropriate, as the first line pharmacological intervention for sialorrhoea, In most clinics people with mild drooling, if identified would be referred to SALT and pharmacological management undertaken. In more severe cases anticholinergics are used, even in PD, where they may lead to serious issues with neuropsychiatric problems and urinary dysfunction. The use of clostridium botulinum toxin serotype A clinically leads to dramatic effects in moderate to severe cases of sialorrhoea, but despite this is only considered rarely in current practice. There is a variety of care pathways across the NHS, with few centres having a well-defined pathway. Sialorrhoea is often seen as a sequela, and occasionally a less important sequela, of underlying neurological disorder or drug treatment (e.g. clozapine),

	and as patients have a tendency either under-report or not be able to report due to the dominance of other aspects of their underlying disease (Ray Chaudhuri *et al.* 2010), the pathway of care can be unclear. This leads to patients being referred to a variety of departments, when they are referred at all. Combined with the previous status of chronic sialorrhoea in adults having no licenced medicines, this has contributed to a varied picture across the UK in terms of the pathway of care and treatment protocols.
• What impact would the technology have on the current pathway of care?	The impact is likely to be manifold: In PD, in early/young onset cases where dribbling may have a devastating effect on social mobility, injection should be the gold standard first line given the uncertain effects of alternative therapies. In later disease, Xeomin becomes the natural choice of therapy, especially when glycopyrronium bromide is unsuitable and longer term management is needed. In palliative PD, MND and other cases with drooling, Xeomin will be considered based on the severity of the problem and its impact. Clarity around where Xeomin fits in the current treatment sequence (e.g. first line pharmacological) will aid the development of local and national pathways of care.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Xeomin has been used off-licence for chronic sialorrhoea for some time, therefore there are healthcare professionals and centres very familiar with its use. The licence recently granted to Xeomin describes dosing and injection protocols in line with current NHS and global practice. The principle change should be *when* Xeomin is used in the treatment pathway (its use is already recommended by NICE). Patients with young onset PD, moderate to severe sialorrhoea, or patients with sialorrhoea where treatment with anticholinergic medicines is contraindicated, should be treated with Xeomin as the first line pharmacological intervention. Assuming that speech and language therapy has been ineffective or is inappropriate to treat moderate/severe sialorrhoea.
• How does healthcare resource use differ between the technology and current care?	There is a massive inequality of care here. In majority of clinics on the NHS there is no provsion for injection treatment of sialorrhoea therefore it is one of the worst managed NMS of PD in spite of its devastating effects on the patient and the carer, In majority of larger specialist centres, there is backup via the SALT services, and some sub optimal management via oral therapies.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Xeomin is currently used in secondary care and specialist clinics. However, as in other indications, a wide variety of healthcare professionals (e.g. physiotherapists and nurses) inject Xeomin when prescribed by an appropriate physician or physiatrist. Also, Xeomin requires no cold chain unlike other preparations of clostridium botulinum toxin of both serotypes currently in clinical use, therefore Xeomin can be (and is, in isolated cases) injected in community clinics by appropriately trained healthcare professionals, although further studies will need to improve the evidence base for this. (Martinez-Poles *et al.* 2018)
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Clostridium botulinum toxin serotype A is regularly used across a number of pathologies, and NHS staff are familiar with its general use. Additional training in the specific injection technique for treating sialorrhoea will be needed, but I doubt this will be onerous. Also, the SIAXI (Jost *et al.* 2019) trial data showed that Xeomin can be injected with or without ultrasound guidance (i.e. via the use of anatomical correlates) with no significant difference in safety. However, it is recommend that localisation of the glands for injection is performed using ultrasound.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Sialorrhoea is a key NMS of PD, high in prevalence (Ray-Chaudhuri et al 2010), bothersome to patients (Politis et al 2010), often not declared to clinicians (Ray-Chaudhuri et al 2010) and is cited as a key unmet need by the evidence based medicine committee of the MDS (Seppi *et al*. 2019) with a global reach. Clinical trials data that is currently available and also personal experience of using this drug shows the great efficacy of this drug in well selected patients. In terms of clinically meaningful changes the ONLY two scales providing objective measurements are DSFS and SCS-PD and neither are used routinely in any clinics., So the meaniful aspects csan be captured by flagging of the problem by NMSQuest (recommended by Parkinson's UK and many societies globally as well as ICHOM, Chaudhuri *et al* 2006) and the NMSS (item 19 Does the patient dribble saliva during the day ? Frequency x Severity + total possible score of 12) in the clinic and changes in the score can provide a reliable measure of the efficacy of the Xeomin in PD. Due to Xeomin's focal administration and mechanism of action, the FDA, EMA, and MHRA have granted licences for Xeomin to be used for treating adults with chronic sialorrhoea due to underlying neurological disorders regardless of aetiology. This is reflective of the broad area of utility of Xeomin, i.e. it is not merely limited to treating sialorrhoea in patients with PD. In MND and other conditions DSFS would be the mainstay. However there are no data on the effect on NMSS from clinical trials It is envisaged that in clinical practice NMSQuest will be used to flag the problem (patient completed self-report) AND NMSS item 19 for efficacy measures along with subjective reports from patients and carer. As noted in NICE Quality Standard QS164 and a NICE briefing paper on Parkinson's Disease (PD), there is a need for better understanding and management of non-motor symptoms (NMS) of Parkinson's Disease. As mentioned above, the variation in

	management of NMS of PD (sialorrhoea is a very common NMS of PD) can lead to sub-optimal care of patients with PD. Improvement in this care by the appropriate use of Xeomin to treat sialorrhoea will deliver clinically meaningful benefits. .
• Do you expect the technology to increase length of life more than current care?	Yes. To take the example of patients with PD again, given that one of the most common causes for emergency admission is chest infection and aspiration pneumonia (e.g. Guneysel *et al.* 2008, Fujioka *et al.* 2016, Braga *et al.* 2014) and that sialorrhoea contributes significantly to these conditions, I expect appropriate management of sialorrhoea with Xeomin to increase length of life.
• Do you expect the technology to increase health-related quality of life more than current care?	In PD if one used a PD specific QoL tool such as PDQ39 or PDQ 8 we expect a major improvement in QoL. Such data is not available The complex underlying nature of the neurological disorders, for which sialorrhoea is a sequela, have a wide variety of QoL impacts, therefore generic HRQoL surveys are likely to be insensitive to. This will to be the case with the use of EQ 5 D which is a generic measure, especially when considering a wide variety of PD cases in addition to cases of TBI and other neurological disorders with sialorrhoea as a sequela. However, the global impression of change Patient reported showed a clear improvement in the trial and this needs to be considered. In addition, the modified Radboud Oral Motor Inventory for Parkinson's also showed a significant imporovement, Domains of this scale have clear questions on social effects as well as personal relevance, issues integral to determination of QoL In the SIAXI trial, where specific disease related measures were used that were sensitive to sialorrhoea itself, improvements in disease state were reported (Jost *et al.* 2019, see also Csikos *et al.* 2018, Jost *et al.* 2019 [Poster 1], Pagan *et al.* 2019, Jost *et al.* 2019 [Poster 2]). These, as discussed above, are correlated with improvements in patient reported quality of life as it pertains to sialorrhoea directly.

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Except where contraindicated, Xeomin has been granted licences by the FDA and EMA for chronic sialorrhoea in adult patients with neurological disorders, regardless of aetiology. Data from SIAXI did show that patients with sialorrhoea due to stroke responded better than those with PD.
The use of the technology	
14. 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 acceptability or ease of use or additional tests or monitoring needed.)	Xeomin has been used off-licence for sialorrhoea for some time. Heterogeneity of care pathways etc aside, I do not anticipate any difficulties specific to this treatment. Since Xeomin can only be injected by trained healthcare professionals, I anticipate no difficulty to patients at all. No concomitant treatments, additional monitoring, or specific clinical requirements are needed.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No health economic rules would be required (as per the company's model). Clinically, other than those related to the appropriateness of treatment, safety, contraindications, and adverse events, no. The use of Xeomin would not require additional testing or any specific stop/start rules. The safety and efficacy profile of Xeomin is well established, and use of Xeomin pre-licence has been extensive, therefore I do not expect any novel rules to be developed for stopping/starting treatment.
16. 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?	Yes. In PD drooling is directly related to dysphagia, a major cause of aspiration pneumonia which is the principle cause of mortality in PD. Drooling is in part associated with dysphagia and as such one would expect considerable health related benefits, particularly related to "hard to reach" populations and symptoms. The rate of admissions for chest infections and aspiration pneumonia have not been considered as part of the QALY, therefore the impact on mortality and morbidity has not been assessed in detail in this HTA. The burden of mortality and hospitalisation in

	PD has been studied (see refs above, and Low *et al.* 2015, Gumber *et al.* 2016), and demonstrates that there is a significant impact on health economies due to chest infection/aspiration pneumonia.
17. 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?	Whilst clostridium botulinum toxin serotypes A and B have long been used to treat sialorrhoea without a licence, there has been low quality evidence for its use (Young *et al.* 2011) in the past. SIAXI is innovative as the largest clinical trial to date regarding the use of any serotype of clostridium botulinum toxin for sialorrhoea. Xeomin is the first and only treatment licenced in this indication and, having a higher grade of evidential support, will lead to wider, and more appropriate, use of Xeomin.
• Is the technology a 'step-change' in the management of the condition?	As Xeomin has been used pre-licence it is not a "step change" in and of itself. However, as mentioned above, given the heterogeneity of care pathways, lack of guidance around treatment selection, and the lack of licenced medication until now, the appropriate positioning of Xeomin is likely to cause a significant improvement of sialorrhoea management. This addresses a significant unmet need in both patient care, and reduction of the mortality and morbidity associated with sialorrhoea from a health economic perspective. Hence, the appropriate use of this technology could be seen to be a step change in the management of sialorrhoea. However, as Xeomin requires no cold chain, there is the opportunity for its use in the community. This does represent a step change, and is a significant difference from other preparations of clostridium botulinum toxin serotype A and B. This lack of cold chain permits ease of access to patients otherwise unable to attend clinic, and given the comparatively straightforward dosing regimen, represents an opportunity to improve patient care in a hitherto underused manner. In addition, Xeomin is free from complexing proteins. Naturally occurring clostridium botulinum is found as a complex of the active neurotoxin and other, clinically inactive, proteins. These complexing proteins are not required for the biological function and clinical benefits of botulinum toxin. Other preparations of botulinum toxin do contain these complexing proteins in varying amounts, forming different complexes. The different proteins, including the active neurotoxin have different immunogenic potential as demonstrated *in vitro* and *in vivo*. The basic science of this immunological aspect of botulinum toxin is uncontroversial, and clinical practice reflects this awareness of the immune consequences of the use of botulinum toxin. To date, in over 2.5 million treatment episodes, no treatment naïve patient has been demonstrated to have secondary loss of response to Xeomin treatment due to the production of antibodies. This aspect of Xeomin as a technology does represent a genuine difference, and hence potential step change in the management of sialorrhoea by potentially preserving the efficacy of treatment long term.

	Xeomin's focal administration and mode of action also limits the problem of polypharmacy.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. There is (as recognised above) a wide variation in the effective management on NMS in PD. Sialorrrhoea is a significant component of this, and is addressed by appropriate use of Xeomin.
18. 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 side effect profile of Xeomin established in SIAXI showed that it has a low rate of deleterious treatment associated side effects. In the case of patients with very compromised swallowing, the decision to treat with Xeomin is one made with care by the treating physician, however, the study data shows that dysphagia derived from the use of Xeomin is not a frequent risk factor. Similarly, rates of xerostomia were low across SIAXI. Both of these important potential side effects are well understood and manageable in clinic.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	The reduction in disease burden as measured by patient/carer reported/clinician observed metrics. In this case, the DSFS represents a simple, clinically meaningful measure of disease severity and correlates well with reported quality of life improvements seen in clinic. Physician's and Patient's GICS scores also track quality of life well.

	As this was a trial with a large number of PD patients, more PD related HRQoL measures could have been employed/modified (Ray Chaudhuri *et al.* 2008). The mROMP results of the trial are, obviously, more related to PD, but other PD related measures (e.g. PDQ-39, UPDRS, NMS-Quest etc) address sialorrhoea specifically, and its impact on HRQoL.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
21. How do data on real-world experience compare with the trial data?	Very favourably. As mentioned above, there is wide use of Xeomin in current clinical practice, published data from real world studies (Martinez-Poles *et al.* 2018) correspond to that from SIAXI. In addition, the wide use of Xeomin in clinical practice prior to the recent grant of licences internationally is well reflected in the trial design, population, dosing, and injection schedule.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No. There are differences of incidence of sialorrhoea between men and women (Ray Chaudhuri *et al.* 2012), and the picture regarding ethnicity and the NMS of PD is complex (Ray Chaudhuri *et al.* 2008).

22b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
23. What factors affect the decision to choose active treatment for sialorrhoea over standard of care? (e.g. severity of sialorrhoea, licensed treatments, patient choice, adverse effects)	Severity of disease is a key determinant of treatment, it is more appropriate to treat patients with moderate to severe sialorrhoea with Xeomin plus standard of care early, than to only use standard of care. The absence of licenced medicines in this area has been part of the reason practice is so heterogeneous. Speech and language therapy and head/neck physiotherapy, for example, have limitations when aiding patients to compensate for moderate to severe sialorrhoea. Another very important factor is that the anticholinergic medications have a wide array of significant side effects due to their systemic administration and mode of action. This means that they are contraindicated in a large portion of the population who would benefit from treatment for sialorrhoea. For example, anticholinergics can cause constipation, urinary retention and confusion, exacerbating existing complications of many neurological conditions, not least deleterious NMS of PD. (Varanese *et al.* 2010, Poirier *et al.* 2016) Also, patients with neurological disorders, particularly PD, are often required to take a comparatively large number of medications. Reducing the issue of polypharmacy (Csoti *et al.* 2019) is one factor in deciding to treat sialorrhoea with Xeomin.
24. How does treatment vary by underlying neurological condition?	In the case of Xeomin, it does not vary. Xeomin has been granted licences by the FDA, EMA, and MHRA for the treatment of chronic sialorrhoea in adults with underlying neurological disorders, regardless of aetiology. This is a reflection of the focal nature of treatment (thus avoiding the systemic side effects associated with other pharmacological treatments), and the specific mechanism of action of Xeomin.
25. What is the current treatment setting for the use of clostridium botulinum toxin products throughout England in the NHS?	As per NG 42 and NG 71, Xeomin is positioned after the anticholinergic medicines have been exhausted (where not contraindicated). It is the company's proposal that Xeomin be positioned either first line as the only licenced treatment, or as a co-first line treatment with the anticholinergics, for use where anticholinergics are specifically contraindicated or their use is unadvisable (e.g. PD patients), and the disease severity is moderate to severe as measured by the DSFS.

26. What are the appropriate outcome measures for measuring clinical benefit of sialorrhoea treatments? Are these correlated with health-related quality of life measurements?	The only two scales providing objective measurements are DSFS and SCS-PD and neither are used routinely in any clinics., So the meaniful aspects csan be captured by flagging of the problem by NMSQuest (recommended by parkinson's UK and many societies globally as well as ICHOM, Chaudhuri et al 2006) and the NMSS (item 19 Does the patient dribble saliva during the day ? Frequency x Severity + total possible score of 12) in the clinic and changes in the score can provide a reliable measure of the efficacy of the Xeomin in PD. NMSS has been validated globally and has now been used in over 50 cinical studies worldwide and has an established cut off regarding burden of scores, 0 = none, 1-4 mild, 6-8 =moderate and > 9 severe. In MND and other conditions DSFS would be the mainstay. However there are no data on the effect on NMSS from clinical trials. It is envisaged that in clinical practice NMSQuest will be used to flag the problem (patient completed self report) AND NMSS item 19 for efficacy measures along with subjective reports from patients and carer. NMSS scores have one of the strongest correlation with HRQol in PD (Martinez-Martin *et al* 2011) The DSFS is a simple to administer clinical measure that accurately assesses disease state, and as mentioned above it correlates well with both objective measures of salivation/salivary control, and HRQoL. The EQ-5D-3L HRQoL measure used in the trial, is not able, in my view, to adequately represent the impact of sialorrhoea on HRQoL. This is unfortunate as there are other measures, specific to sialorrhoea (mentioned above), that could have better elucidated the HRQoL benefits of Xeomin. The principle reasons for this insensitivity are due to the complex nature of the underlying neurological conditions for which sialorrhoea is a sequela. Xeomin is obviously not a direct treatment for, for example, PD. Xeomin treats one non-motor symptom of PD (and sialorrhoea as a sequela of other equally complex neurological disorders). For example, in PD depression can be caused by factors unrelated to sialorrhoea, and as such responses to this domain of the EQ-5D will be confounded by the multifactorial aspects of the underlying aetiology of depression. The same will apply to other domains of the EQ-5D like the usual activities of daily life (compromised by NMS and MS of PD, for example the on/off pattern of treatment for PD), and self-care (also confounded by the NMS and MS of PD, for example, tremor). However, the DSFS tracks well with HRQoL and the mROMP and GICS data reflect the specific improvement of HRQoL due to sialorrhoea better than does the EQ-5D in this instance.

	Due to Xeomin's focal administration and mechanism of action, the FDA, EMA, and MHRA have granted licences for Xeomin to be used for treating adults with chronic sialorrhoea due to underlying neurological disorders regardless of aetiology. This is reflective of the broad area of utility of Xeomin, i.e. it is not merely limited to treating sialorrhoea in patients with PD
27. Would ultrasound guidance be used during the injection procedure?	As data from SIAXI showed the use of US guidance in the treatment of sialorrhoea is advisable but not necessary. However, best practice would be to use ultrasound guidance.

Key messages

28. In up to 5 bullet points, please summarise the key messages of your statement.

- Xeomin is a widely used therapy that has now received licences across the globe for the treatment of chronic sialorrhoea in adults due to underlying neurological disorders, with no restriction on the aetiology. This is due to Xeomin's safety and efficacy profile, mode of action, and focal administration.
- Xeomin is the first and only product licenced for chronic sialorrhoea due to neurological disorders in adults, a key current unmet need in the management of PD and some other long term conditions, where little evidence of efficacy of therapies exists. As such, Xeomin represents an important treatment that addresses a significant unmet patient need in the management of sialorrhoea as a NMS of PD, and as a sequela of other neurological disorders.
- Sialorrhoea in PD, can be effectively signposted by the use of the widely used NMSQuest and efficacy measured by item 17 score changes oin the NMSS (takes 2-3 min to score) . In addition, the DSFS as a measure of disease state, and measure of the impact of disease on a patient is appropriate and correlates well with both objective measures of sialorrhoea and the HRQoL impact of sialorrhoea (also shown by the mROMP and GICS data in SIAXI). The EQ-5D is, in this case, insufficient to detect changes in HRQoL due to sialorrhoea alone, and is confounded by the complex aetiology of the matters addressed by its various domains.
- There is a significant mortality and morbidity associated with poor management of drooling. Sialorrhoea is often associated with significant dysphagia, which a key risk factor for aspiration pneumonia/chest infection, particularly in PD patients. Xeomin as a treatment for sialorrhoea addresses this unmet need.

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Clinical expert statement

Clostridium botulinum neurotoxin type A for treating chronic sialorrhoea [ID1150]

Thank you for agreeing to give us 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.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- 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 13 pages.

About you	
1. Your name	**Dr Tabish Saifee**
2. Name of organisation	**Association of British Neurologists**

3. Job title or position	**Consultant Neurologist**
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 this condition? ☐ a specialist in the clinical evidence base for this condition 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 didn't submit one, I don't 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

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	
8. 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.)	
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	

10. How is the condition 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?	
11. 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 clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
12. 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?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
14. 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 acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
16. 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?	
17. 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?	
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	

19. 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?	
20. Are you aware of any relevant evidence that might	

not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23. What factors affect the decision to choose active treatment for sialorrhoea over	

standard of care? (e.g. severity of sialorrhoea, licensed treatments, patient choice, adverse effects)	
24. How does treatment vary by underlying neurological condition?	
25. What is the current treatment setting for the use of clostridium botulinum toxin products throughout England in the NHS?	
26. What are the appropriate outcome measures for measuring clinical benefit of sialorrhoea treatments? Are these correlated with health-	

related quality of life measurements?	
27. Would ultrasound guidance be used during the injection procedure?	

Key messages

28. In up to 5 bullet points, please summarise the key messages of your statement.

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Clostridium botulinum neurotoxin type A for treating chronic sialorrhoea: A Single Technology Appraisal.

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Date completed	Date completed (15/04/2019)

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 17/156/06.

Declared competing interests of the authors

None of the authors has any conflicts of interest to declare.

Acknowledgements

We would like to thank Becky Pennington, ScHARR, for providing comments on the draft report and Andrea Shippam, Programme Manager, ScHARR, for providing administrative support and in preparing and formatting the report. We would also like to thank Dr Paul Cooper, Consultant Neurologist, Salford Royal NHS Foundation Trust and Honorary Senior Lecturer, University of Manchester, Dr Akif Gani, Consultant Stroke Physician and Geriatrician, Newcastle upon Tyne Hospitals NHS Foundation Trust, and Dr Donald Grosset, Consultant Neurologist and Honorary Professor at the University of Glasgow, for clinical advice within the project. Professor John Brazier, Dean of ScHARR, and Professor Allan Wailoo, Professor of Health Economics, ScHARR, provided advice related to the sensitivity of the EQ-5D.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Stevenson M, Ren S, Simpson E, Metry A, Orr M, Wong R. Clostridium botulinum neurotoxin type A for treating chronic sialorrhoea: A Single Technology Appraisal. School of Health and Related Research (ScHARR), 2019.

Contributions of authors

Emma Simpson summarised and critiqued the clinical effectiveness data reported within the company's submission. Matt Stevenson and Andrew Metry critiqued the health economic analysis submitted by the company. Shijie Ren and Martin Orr critiqued the statistical analyses presented in the company's submission. Ruth Wong critiqued the company's search strategy. All authors were involved in drafting and commenting on the final report.

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Abbreviations

AEs	Adverse Events
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
CBTA	Clostridium botulinum toxin A
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence Interval
CS	Company Submission
CSR	Clinical study report
DSFS	Drooling Severity and Frequency Scale
EP	Extension period (of SIAXI trial)
EQ-5D-3L	Euroqol 5-dimensions 3-levels
ERG	Evidence Review Group
GICS	Global Impression of Change Scale
ICER	Incremental Cost Effectiveness Ratio
IQR	Inter Quartile Range
ITT	Intention to treat
LCMM	Latent Class mixed models
mITT	Modified intent to treat
MMRM	mixed model repeated measurement analysis
MP	Main period (of SIAXI trial)
mROMP	Modified Radboud Oral Motor Inventory for Parkinson's Disease
NICE	National Institute for Health and Care Excellence
QA	Quality Assessment
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
SAEs	Serious adverse events
SD	Standard Deviation
SES	Safety Evaluation Set
SIAXI	Trial name = Clinical Study to Investigate the Efficacy and Safety of Two Dose Levels of NT 201 Versus Placebo in Treating Chronic Troublesome Sialorrhoea in Various Neurological Conditions
SoC	Standard of care
STA	Single Technology Appraisal
UPDRS ADL	Unified Parkinson's Disease Rating Scale activities of daily life
uSFR	Unstimulated salivary flow rate

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company provided an appropriate description of chronic sialorrhoea (excessive drooling) and the anticipated positioning of clostridium botulinum toxin A (CBTA) (Xeomin®) in the treatment pathway, however, the company did not include references to the caveats published in NICE Guideline 62 related to the potential detrimental effects of injecting botulinum toxin A into an incorrect site. CBTA costs in the region of £425 per annum excluding administration costs.

1.2 Summary of clinical effectiveness evidence submitted by the company

Aside from one small crossover trial, the key clinical effectiveness evidence for CBTA was based on one randomised controlled trial (RCT), named SIAXI. For 16 weeks of follow-up in the main period (MP), SIAXI had three treatment groups: placebo n=36; CBTA 100U n=74; and CBTA 75U n=74. The 75U regimen is not part of marketing application and is not considered in the Evidence Review Group (ERG) report. An extension period followed with the potential for an additional 48 weeks of CBTA, resulting in a maximum follow-up of 64 weeks.

SIAXI showed a statistically significantly (p=0.004) greater reduction in unstimulated salivary flow rate for CBTA 100U compared with placebo, at four weeks' follow-up of the SIAXI MP. This difference remained statistically significant throughout the MP. Throughout the extension period, patients treated with CBTA 100U continued to have lower uSFR than at baseline.

The Participant's Global Impression of Change Scale showed a statistically significant advantage for CBTA 100U over placebo (p=0.002) at 4 weeks' follow-up of the SIAXI MP. This difference remained statistically significant to week 12 of the MP.

The most commonly reported adverse events (AEs) in the CBTA 100U group were tooth extraction, dry mouth, diarrhoea and hypertension. None of the serious adverse events (SAEs) in the SIAXI MP was considered treatment-related.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG believes that all available RCTs informing on the clinical effectiveness of CBTA were included in the company submission. The study selection criteria of the review were consistent with the decision problem in the NICE final scope. The quality of the CBTA RCTs was assessed using well-established and recognised criteria.

Fifteen RCTs of comparators were identified, but no network meta-analysis was conducted, which was reasonable given the heterogeneity between trials.

1.4 Summary of cost effectiveness submitted evidence by the company

The model submitted was clear and generally well programmed, with minor errors amended in the clarification process along with structural changes. The company modelled three-severity health states of sialorrhoea, which were based on the drooling severity and frequency scale (DSFS) score. These were: resolved / mild (DSFS scores of 2 and 3); moderate (DSFS scores of 4-6); and severe (DSFS scores of 7-9). Transitions between health states for CBTA and standard of care (SoC) were modelled using the observed data from SIAXI continuity corrected for small patient numbers with discontinuation rates for CBTA taken from SIAXI. Corresponding values for glycopyrronium bromide, a widely used anticholinergic were estimated from published data and clinical opinion. The base case utility values for sialorrhoea severity state were sourced from a NICE clinical guideline, which focussed on patients at a markedly different age than those recruited to SIAXI and with a different underlying disease, although EuroQol five dimensions three-level (EQ-5D-3L) data from SIAXI was used in a scenario analysis. The time horizon in the base case was 10 years, with discounting of both benefits and costs at 3.5% per annum. The company's base case results suggested that CBTA was cost-effective compared with both SoC and glycopyrronium bromide. The incremental cost-effectiveness ratios (ICERs) for CBTA compared with SoC were £9,200 per QALY gained when treating patients with severe sialorrhoea and £10,100 per QALY gained when treating patients with moderate sialorrhoea. Compared with glycopyrronium bromide, CBTA was estimated to provide more health at a reduced cost, irrespective of sialorrhoea severity level.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The key difference between the approach undertaken by the company and that preferred by the ERG is related to the utility values assigned to each of the sialorrhoea severity states. The ERG believes that it has not been conclusively proven that the EQ-5D-3L is insensitive to sialorrhoea and therefore that the EQ-5D data from the pivotal SIAXI should be used in the base case. This reduces the difference in utility between severe sialorrhoea and mild / resolved sialorrhoea from 0.234 in the company's base case to 0.045 in the ERG's analysis of the SIAXI trial data.

A number of other alternative approaches were preferred by the ERG within the base case but these had much less impact on the ICER. These included altering: the administration costs of CBTA; the way that discontinuations were modelled in relation to both lack of efficacy and other reasons; the method of applying a continuity correction; the standardised mortality rate assumed; the acquisition cost of glycopyrronium bromide; and the variance associated with the mean values of EQ-5D-3L.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The search of CBTA RCTs was comprehensive and it is believed that no relevant available RCTs of CBTA were excluded. The included CBTA RCT was of good methodological quality.

The submitted mathematical model was of good quality. The company responded well to the clarification questions raised and provided a revised model and undertook the analyses requested.

1.6.2 Weaknesses and areas of uncertainty

Apart from one small crossover study with no pre-crossover data, only one RCT of CBTA + SoC was available. This RCT used a comparator of placebo, not an anticholinergic therapy. The effectiveness of comparator interventions was studied in only a few poor quality RCTs of short duration that did not allow an indirect comparison between CBTA + SoC and anticholinergics + SoC.

The company make a case that the EQ-5D-3L is insensitive to the improvement of chronic sialorrhoea, although the ERG does not believe that this has been definitively proven. The utility values used in the company's base case are believed to be inappropriate as they are in a markedly different population, are not evidence-based and the estimated change in utility may be confounded due to the underlying condition.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

As stated in Section 1.5 the ERG preferred alternative assumptions in the base case on multiple occasions to the company, although one change had markedly more influence on the ICER than the others did. This was changing the utility values assigned to each sialorrhoea severity state to those derived from the EQ-5D-3L data collected in SIAXI which involved using a latent class mixed model. This approach increased the deterministic cost per quality-adjusted life year (QALY) gained of CBTA + SoC compared with SoC from £9,162 (a cost increase (ΔC) of £3,066 and QALY gain (ΔQ) of 0.335) to £45,275 (a cost increase of £3,066 and QALY gain of 0.068) for patients with severe sialorrhoea. For patients with moderate sialorrhoea the change was from £10,130 (ΔC £3,125; ΔQ 0.309) to £49,329 (ΔC £3,125; ΔQ 0.063). When implementing the remaining changes, the deterministic cost per QALY changed to £44,492 (ΔC £2,353; ΔQ 0.053) for patients with severe sialorrhoea and to £50,955 (ΔC £2,498; ΔQ 0.049) for patients with moderate sialorrhoea. The corresponding probabilistic values were £41,335 (ΔC £2,357; ΔQ 0.057) for patients with severe sialorrhoea and £48,127 (ΔC £2,541; ΔQ 0.053) for patients with moderate sialorrhoea. For completeness, analyses were undertaken for the combined severity population, which produced a deterministic ICER of over £47,000 (ΔC £2,419; ΔQ 0.051) and a probabilistic ICER of over £45,000 (ΔC £2,455; ΔQ 0.054).

To acknowledge that it may be plausible that the EQ-5D-3L is insensitive to chronic sialorrhoea improvement, a threshold analysis was undertaken which increased the utility difference between the resolved/mild health state and the moderate health state and increased the utility difference between the moderate health state and the severe health state by a common factor. This factor was increased until the ICER of CBTA + SoC compared with SoC was equal to £20,000 per QALY gained with the analyses undertaken for a moderate group of patients and for a severe group of patients. The multiplication factors required were 2.22 for patients with severe sialorrhoea, 2.55 for patients with moderate sialorrhoea and 2.37 for patients with severe or moderate sialorrhoea to obtain ICERs of £20,000 per QALY gained. These factors reduced to 1.48, 1.7 and 1.58 respectively assuming a threshold of £30,000 per QALY gained.

In the ERG analyses CBTA + SoC dominated glycopyrronium bromide + SoC. In severe patients the probabilistic outputs were ΔC -£4,557 and ΔQ 0.034, with the corresponding values for moderate patients being ΔC -£5,093 and ΔQ 0.028 As such, if a clinician were considering the use of glycopyrronium bromide then it is anticipated that the use of CBTA + SoC instead would be associated with increased patient health and a reduction in expenditure.

2 BACKGROUND

2.1 Disease background

Sialorrhoea is defined as the unintentional loss of saliva from the mouth, and it can develop associated with mainly neurological underlying aetiologies. Negative impact on the patient's health-related quality of life (HRQoL) may range from poor oral hygiene and bad breath to aspiration pneumonia in some instances. Within the company submission (CS)[1], there is an acceptable summary of sialorrhoea, which details the definition, underlying causes, pathophysiology, disease burden, and epidemiology.

There are no current treatment guidelines for sialorrhoea per se. However, treatment considerations concerning sialorrhoea because of certain neurological conditions were included in several NICE clinical guidelines including NG71, NG62, and NG42.[2, 3] The Parkinson's disease guideline (NG71) recommends considering glycopyrronium bromide after failure on non-pharmacological management (such as speech and language therapy). If glycopyrronium bromide is not effective, not tolerated or contra-indicated NG71 recommends that a physician should consider referral to a specialist service for botulinum toxin A, such as Clostridium botulinum toxin A (CBTA). Both the cerebral palsy in under 25s guideline (NG62) and motor neurone disease guideline (NG42) state that anticholinergic therapies should be considered as treatments regardless of whether non-pharmacological management has failed.

Clinical advice provided to the ERG stated that within Parkinson's disease the positioning of botulinum toxin A within NG71 was driven by the fact that no botulinum toxin A product was licensed for use in such patients. It was strongly suggested by the ERG's clinicians that if a botulinum toxin A product had been licensed at the time the guidelines were written, as CBTA (Xeomin®) now is, then this would have been the recommended first-line treatment in the NICE guideline after non-pharmacological treatment. The positioning of a botulinum toxin A product before anticholinergics would be due to the adverse events associated with glycopyrronium bromide (dry mouth, agitation / nervousness, constipation, nausea and potential for cognitive decline) and the belief that a botulinum toxin A product was at least as effective as anticholinergics.

NG62 did include a caveat related to the use of botulinum toxin A injections stating, "*The Committee were advised that over the longer term, the investment to increase the supply of specialists to administer botulinum toxin type A could be considered cost-effective. However, the Committee strongly advised that if there were to be an investment of resources in this area, it would be extremely difficult to recruit specialists willing to undertake the procedure because of the potential detrimental effects on the nervous system if the wrong site is injected. As a result, the Committee concluded that it would be unrealistic to increase the supply of specialists to cope with the increase in demand as those specialists would conclude that the benefits would only outweigh the risks in severe drooling cases i.e. those cases when botulinum toxin type A currently displaces glycopyrrolate. The Committee also stated that the evidence*

on those risks was not provided by the literature, but has been seen during their clinical experience." The ERG consulted its clinical advisors to enquire about the potential harm that could result from misplaced injections of CBTA and received the following advice.

One clinician suggested that balancing up the risks of injecting delicate sites with the benefits might make clinicians more cautious about injecting patients with mild or moderate sialorrhoea. This was echoed by another clinician who stated that whilst specialists tend to use new/perceived higher risk procedures more sparingly and predominantly in higher severity cases, as there is the potential for risks associated with breathing and swallowing difficulty. The clinician anticipated that as experience increases and safety/efficacy is demonstrated, that clinicians would begin to start using these in progressively less severe cases. This expert also stated that clinicians already trained in parallel clinical aspects of care would not find it that onerous to be trained in CBTA injections as they are already well aware of neuro-anatomy but commented that whilst there is very little in the literature related to complication rates that there is a larger risk with this procedure than muscle or cosmetic injections such as swallowing complications and dry mouth. However, by using low doses, clear anatomical landmarks alongside protocols/procedures and with potential nearside ultrasound imaging adjuncts these risks would be minimised. The clinician further commented that establishing a regional-based centre to perform CBTA injections would not be unrealistic. The third clinician believed it would be possible the parotid gland but unlikely to cause significant harm, with more risks being associated with injections into the submandibular glands and did not agree with the concerns stated in NG62.

All clinicians believed that ultrasound was likely to be used widely if CBTA became a common treatment for chronic sialorrhoea.

2.2 The technology and the company's anticipated positioning of Clostridium botulinum toxin A

CBTA is marketed by Merz Pharma UK for the treatment of chronic sialorrhoea regardless of the cause of the sialorrhoea, although it is anticipated that a large proportion of such patients would have an underlying cause of Parkinson's disease or stroke. A description of CBTA is provided in Section 1.2 of the CS. The product is available as powder for injection. The recommended total dose per treatment session is 100 units (U), typically every 16 weeks. One total dose is divided between four injection sites involving two pairs of salivary glands; namely the parotid and submandibular glands. Generally, these injections are administered by physicians with suitable qualifications and are guided by either ultrasound imaging or observing surface anatomical landmarks.

Despite NICE recommendations to consider anticholinergics use in the first-line management, lack of clinical evidence supporting their efficacy and adverse events associated with anticholinergics limits

their use. The company stated that, according to feedback they received from clinicians, many (proportion not stated) patients do not receive active therapy for their sialorrhoea management, and rely only on non-pharmacological management including bibs, as well as speech, language and occupational therapy. For the rest of patients, oral glycopyrronium bromide is the most prescribed active treatment, and the company considered it as the most relevant active comparator to CBTA.

Figure 3 in the CS, reproduced in Figure 1 depicts the company's intended positioning of CBTA among its comparators. This figure is potentially confusing as the mathematical model does not consider second-line treatment with an active drug but evaluates CBTA plus SOC; glycopyrronium bromide (or an alternative anticholinergic treatment) plus SOC; and SOC alone, as first-line treatments for sialorrhoea. Patients discontinuing active treatment would revert to SOC only. The ERG has redrawn the positioning of CBTA plus SOC in Figure 2 to match the economic analysis.

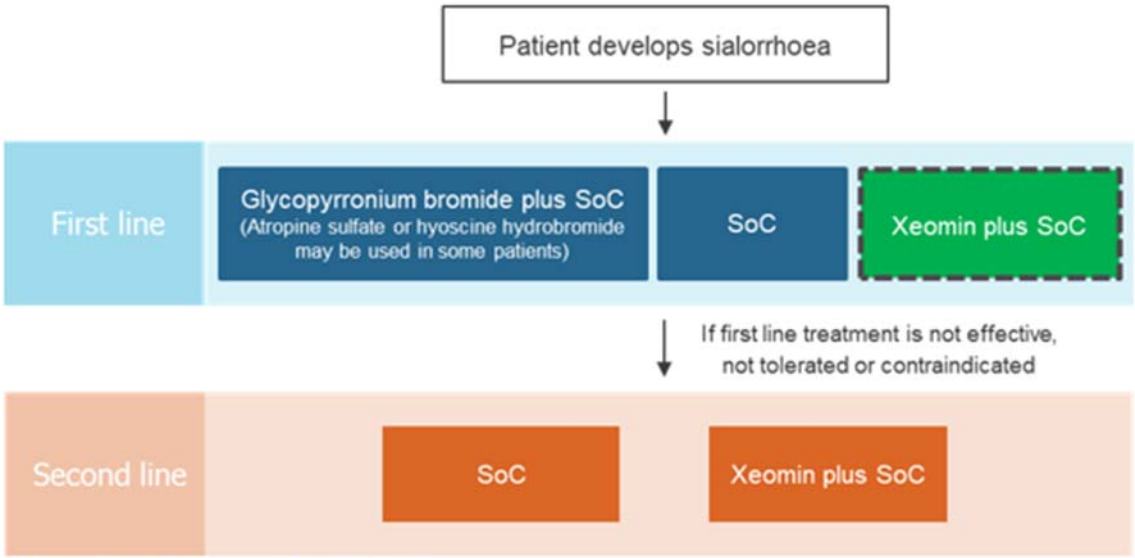
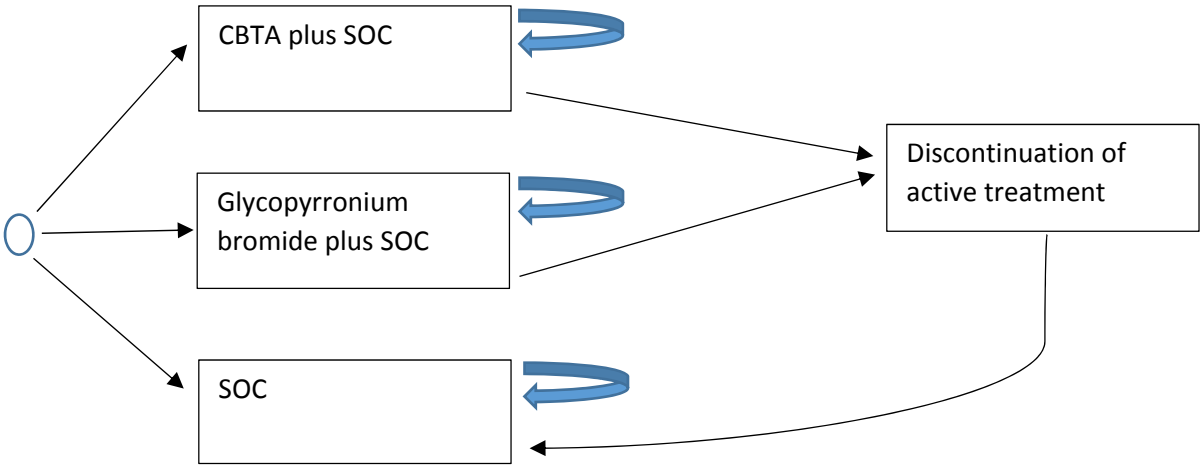


Figure 1: The company's anticipated positioning of CBTA within the current clinical pathway



Patients can die from any health state at all cycles of the model. CBTA: Clostridium botulinum A, SOC: standard of care.

Figure 2: The treatment pathways modelled within the economic evaluation

2.3 Critique of company's definition of decision problem

The ERG has assessed the company's definition of the decision problem against guidance provided in the NICE reference case.[4] A critique of how the modelling undertaken adheres to the NICE reference case is provided in Section 4.3.2.

Table 1: ERG critique of the company's definition of the decision problem

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The ERG notes that the CS includes patients with sialorrhoea in general regardless of the underlying cause. In addition, adult patients with dysphagia were not included.
Comparator(s)	As listed in the scope developed by NICE	The company's model compares CBTA against glycopyrronium bromide, which the company claims is the most used anticholinergic therapy. Other anticholinergics were considered in the scenario analysis. The model also includes non-pharmacological standard management as a comparator.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health gains accrued by patients are modelled in terms of QALYs gained
Perspective on costs	NHS and PSS	Costs were considered from an NHS and PSS perspective

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

3.1.1 Searches

The company performed one clinical effectiveness search to identify all clinical and safety studies of CBTA and its pharmacological comparators (anticholinergic therapies such as glycopyrrolate, scopolamine and tropicamide) for the treatment of sialorrhoea.

The company conducted the systematic literature search on the 14th August 2018 in several electronic bibliographic databases including MEDLINE [via Ovid], MEDLINE in Process [via Ovid], Embase [via Ovid], Cochrane Database of Systematic Reviews [via Wiley], Cochrane Central Register of Controlled Trials [via Wiley], and the Database of Abstract of Reviews of Effect [via CRD]. The company carried out a manual search of four conference abstracts books (American Academy of Neurology, Association of British Neurologists, European Academy of Neurology, International Congress of Parkinson's Disease and Movement Disorders) covering the period from 2016 to 2018. The company searched one ClinicalTrials.gov register and supplementary searches include scanning of bibliographies of relevant reviews and meta-analyses.

In Appendix D of the CS, the company reported full literature search strategies for the disease area sialorrhoea combined with an RCT sensitive study design and publication exclusion filters. The ERG considers that search strategies are sufficiently comprehensive to retrieve important citations relating to all eligible studies.

The ERG did not carry out searches for non-RCT or adverse events searches of studies reporting the risk of death associated with stroke or Parkinson's disease.

3.1.2 Inclusion criteria

The eligibility criteria applied in the selection of evidence for the clinical effectiveness review, presented in CS Section B.2.1 and CS Appendix D Table 7 (and clarification response A7), were considered by the ERG to be reasonable and consistent with the decision problem outlined in the final NICE scope.[5]

The included study design was limited to RCTs (Section B.2.1 of CS). This is standard practice to restrict to high quality study designs where they are available. Study selection was conducted by two independent reviewers (CS Appendix D.4) as is good practice.

Two RCTs of CBTA were identified (Section B.2.1 of the CS) that met the eligibility criteria of the review, SIAXI[6 7 8-10] and NCT01653132. [11 12] SIAXI was a parallel-group multicentre RCT, and NCT01653132 was a crossover RCT with nine patients in the analyses.

3.1.3 Critique of data extraction

Data were extracted by one reviewer and checked by a second reviewer (CS Appendix D.4) in accordance with good practice. Data extracted for the SIAXI trial were checked by the ERG against the relevant publications,[8-10] the clinical trials registry[6] or the clinical study report (CSR)[7] where applicable, and found to be accurate.

3.1.4 Quality assessment

Quality items assessed by the company (CS Appendix D6 Table 11) were taken from the Centre for Reviews and Dissemination guidelines for undertaking reviews in health care. These are standard and appropriate criteria for assessing the risk of bias in RCTs.[13]

The ERG checked the quality assessment of the CBTA trials from the CS against their publications (Table 2). SIAXI is, at the time of writing, published only as conference abstracts, and more detail would be expected from a full publication. The ERG checked the SIAXI CSR[7] additionally.

The generation of randomisation sequences was by computer programme in NCT01653132[12] [redacted] Allocation concealment was unclear in NCT01653132[12], and [redacted]

Both the NCT01653132 study and the SIAXI RCT were balanced in terms of patient baseline characteristics, and had no unexpected imbalances in drop-outs.[6, 11] Both trials were blinded,[6, 11] reducing the risk of bias that may be seen especially with patient reported outcomes. One of the co-primary outcomes of SIAXI was unstimulated salivary flow rate (uSFR), an objective measure of lower risk of bias than patient reported outcomes, as was the primary outcome of NCT01653132, which was change in saliva weight.[6, 11]

Neither trial provided an intention to treat (ITT) analysis. In the NCT01653132 trial, one out of ten randomised patients did not provide data.[12] SIAXI conducted a modified ITT (mITT), including, for the primary outcome, participants who were treated and had at least the baseline value uSFR (CS Section B.2.4): this meant 73/74 of the CBTA 100U group, and 36/36 of the placebo (PBO) group, provided data for the primary outcome. Where there were missing data, these were accounted for using the mixed model repeated measurement analysis (MMRM) approach (CS Section B.2.4).

Table 2: Quality Assessment (QA) by CS and by ERG (CS QA from Appendix D6 Table 11)

	SIAXI NCT0209173[6 7 8-10]		NCT01653132[11 12]	
	QA from CS	QA by ERG	QA from CS	QA by ERG
Was the randomisation method adequate?	Unclear – no details were provided	Unclear from publications [redacted]	Yes - subjects were randomised by the study pharmacist using a computer-generated schedule	Yes, computer generated randomisation
Was the allocation adequately concealed?	Not reported – no details were provided on allocation concealment	Unclear from publications [redacted]	Unclear – the study reports that it concealed allocation, but provides no further details	Unclear
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes – baseline demographics and disease characteristics were similar between treatment groups	Yes	Yes – groups were similar in terms of baseline characteristics	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes – study described as double blind	Yes, the main phase (MP) of the study was blinded, participants and investigators (who were also outcome assessors)	Yes – study described as double blind	Yes, participants and outcomes assessors blinded
Were there any unexpected imbalances in drop-outs between	No – only two patients dropped out, and these were deemed unrelated to the study medication.	No, 11 patients did not complete the MP: 4 PBO; 5 CBTA 75U; 2 CBTA	No – only one patient dropped out, and reasons were provided. This	No, one patient dropped out to start treatment for

groups? If so, were they explained or adjusted for?	Analyses were adjusted to exclude these patients from the final analyses.	100U. Reasons for this were given (Table 7). Data analysis accounted for all but 2 patients who were not in full analysis set (FAS) which was the subset of participants who were treated and had at least the baseline value of uSFR.	patient was subsequently excluded from the analyses	tremor and was excluded from the analyses
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No – all predefined outcomes were reported	No	No – all predefined outcomes were reported	No
Did the analysis include an intention-to-treat analysis?	No – the FAS was used	No, mITT using the FAS	Unclear – no details were provided	No, one subject dropped out after first injection and was not included in analyses
Did the authors of the study publication declare any conflicts of interest?	Yes – authors declared the study was sponsored by Merz Pharmaceuticals GmbH, who developed the drug under investigation, and declared any other support that they received	Yes, funding source Merz Pharmaceuticals GmbH and author conflicts stated [9]	Yes – all authors disclosed any potential conflicts of interest	Yes, funding source Merz Pharmaceuticals LLC and author conflicts stated [12]

3.1.5 Evidence synthesis

Section B.2.8 of the CS states that the crossover study NCT01653132 was deemed to have too small a sample size (n=9 analysed) to pool with SIAXI.

Both trials included the intervention CBTA 100U although there was a difference in delivery, with SIAXI administering 30U (0.6 mL) in the parotid glands and 20U (0.4 mL) in the submandibular glands, respectively, per side. In NCT01653132 (the crossover trial), 20U were injected into each parotid and 30U to each submandibular gland.

The results reported for NCT01653132 did not include pre-crossover results.[12] Although a one-month washout period was used, the authors state they could not conclusively exclude carry-over effects.[12] In this case it can't be certain that the results of crossover trial are comparable with those from a parallel group trial[14] and so the decision not to conduct a meta-analysis of NCT01653132 and SIAXI was considered by the ERG to be appropriate.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 CBTA trials

Two RCTs of CBTA were identified that met the eligibility criteria of the review, SIAXI and NCT01653132. SIAXI was a parallel-group multicentre RCT, and NCT01653132 was a crossover RCT with nine patients in the analyses. Due to the small sample size, the CS did not use the results of NCT01653132 for the cost-effectiveness modelling, although the CS clarification response[15] provided effectiveness and safety results of NCT01653132.

One trial of CBTA, NCT01565395, was identified by the CS search but then excluded. In clarification response A6[15] the company explains that this was planned as an arm of the NCT01653132 study with amyotrophic lateral sclerosis patients, but could not recruit these patients and so NCT01565395 was withdrawn. The ERG believes that all relevant RCTs of CBTA were included in the CS.

Trial characteristics of the two CBTA trials meeting the inclusion criteria are shown in Table 3. Eligibility criteria differed between trials, with the crossover trial enrolling Parkinson's disease / Parkinsonism patients, whilst the SIAXI trial also included stroke and traumatic brain injury patients. SIAXI was a parallel-group multicentre RCT for the main period (MP) of the trial. Following the MP, patients could be enrolled (based on clinical need and lack of AEs) in the extension period (EP) during which they either stayed on their allocated dose of CBTA, or patients from the placebo group were randomised to either CBTA 100U or CBTA 75U. Full eligibility criteria for SIAXI (MP and EP) are provided in CS Appendix L.

Primary outcomes for both trials are shown in Table 3. NCT01653132 measured saliva weight with a pre-weighed cup for 5 min, calculated over a mean of two assessments.[12] Descriptions of the outcomes assessed in SIAXI are shown in Table 4. Baseline characteristics of the trials are shown in Table 5 and Table 6. Clinical advice suggests that the demographics are quite representative of patients that would be seen in UK practice, although the Parkinson's disease patients in the trials may be a little younger (by around 5 years).

Marketing authorisation is being considered for CBTA 100U, not 75U, according to the CS (CS Table 2). Thus, the results of the SIAXI CBTA 75U trial are not included in the ERG report. Results for the SIAXI CBTA 75U treatment group are reported in the CS.

Table 3: Trial characteristics of CBTA trials (CS section B.2.3.1)[6]

Trial name (and publications)	Trial design	Population	Intervention and comparator	Primary outcome
SIAXI (NCT02091739) https://clinicaltrials.gov/show/nct02091739 2014.[6] Blitzer 2017[8] Blitzer 2018[9] Jost 2018[10]	Phase III, prospective, randomised, double-blind, parallel-group, multicentre, Germany (53 patients) and Poland (131 patients) Main period (MP) (16 weeks) placebo-controlled, Extension period (EP) (48 weeks from end of MP)	Parkinson's Disease / Parkinsonism, stroke, TBI Chronic (3+months) troublesome sialorrhoea defined as: Drooling Severity and Frequency Scale (DSFS) sum score 6 or greater; 2 or greater points each item of DSFS; and 3 or greater points Drooling item of mROMP	Four injections into bilateral parotid and bilateral submandibular salivary glands per treatment cycle (16 ±2 weeks) 1) CBTA 100 U N=74 2) CBTA 75 U N=74 3) PBO N=36	Co-primary outcomes, MP: uSFR; Global Impression of Change Scale (GICS)
NCT01653132 https://clinicaltrials.gov/show/nct01653132. 2012[11] Narayanaswami 2016[12]	Phase II randomised, double-blind, placebo-controlled crossover trial, single centre, US-based	Parkinson's Disease / Parkinsonism Sialorrhoea that patients, their families or treating physicians define as troublesome	Four injections into bilateral parotid and bilateral submandibular salivary glands	Objectively Measured Salivary Weight

Narayanaswami 2015[16]	3 months followed by 1- or 2-months washout, then crossover with 3 months follow-up	Swallowing function: Functional Oral Intake Scale of 5+	1) CBTA 100 U followed by PBO N=5 2) PBO followed by CBTA 100 U N=5 (of which 4 remained in study and were analysed)	

Table 4: SIAXI trial outcomes

	Outcome measures used (CS Table 4)	Definitions [CS][6]
Co-primary outcomes, measured from baseline to week 4 of main period	uSFR	Assessed by weighing of dental rolls soaked with saliva over 5 minutes and then procedure was repeated after 30 minutes and the average of the 2 results for flow rate was calculated.
	Participant's GICS	7-point Likert scale that ranged from -3 = very much worse to +3 = very much improved and was applicable for participant and caregiver. If the participant was not able to answer then carer's rating was to be recorded instead of participant's rating and the participant's rating was left blank.
Secondary outcomes	uSFR change from baseline to Week 8 and 12	uSFR as above
	Participant's GICS at Weeks 1, 2, 8, and 12	GICS as above
	DSFS	2 subscales: a 4-point Likert scale for 'drooling frequency', ranging from 1 (never) to 4 (constantly), and a 5-point Likert scale for 'drooling severity', ranging from 1 (dry) to 5 (profuse). The DSFS is the sum score of the two subscales, ranging from 2 (best) to a maximum (worst) score of 9. The time period used for each evaluation was "over the past week". [definition from CS]
	EQ-5D-3L	The 3-level version of the EuroQol five-dimension measure of HRQoL

	Modified Radboud Oral Motor Inventory for Parkinson's Disease (mROMP)	A 24-item questionnaire where each item is measured on a 5-point Likert scale in three parts: I = speech, II = swallowing symptoms and III = drooling. Part II (swallowing symptoms) was administered as a safety assessment. Parts I and III were administered as efficacy assessments [definition from CS]
	Adverse events (AEs) and serious adverse events (SAEs)	Treatment emergent AEs SAEs were defined as those with onset or worsening at or after the first injection, up to 16 weeks after, the last study visit or the first injection of the EP (CS Section B.2.10.1). Treatment related adverse events (those considered related to treatment). Adverse events of special interest (AESIs); those that possibly indicated toxin spread* (CS Section B.2.10). Serious adverse events (SAEs); those that resulted in death, were life threatening, or required in-patient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, and/or consisted of any other medically important condition (CS Section B.2.10.1)

*AESIs are listed in CS Table 36, and included dysphagia, dry mouth, dysarthria, bradycardia and eyelid ptosis.

Table 5: Baseline characteristics SIAXI trial Main Period and Extension Period (adapted from CS Table 5 and CS Appendix Table 24)[6, 7]

	MP		EP
Characteristics	**CBTA 100 U (N=74)**	**Placebo (N=36)**	**CBTA 100 U (N=89)**
Sex n (%)			
Male	52 (70.3)	28 (77.8)	[redacted]
Female	22 (29.7)	8 (22.2)	[redacted]
Age (years)			
Mean (SD)	66.0 (11.6)	63.5 (10.6)	[redacted]
Median	67.5	64.0	[redacted]
Min, max	21, 80	23, 80	[redacted]
Age group n (%)			
18-64 years	28 (37.8)	19 (52.8)	[redacted]
65-84 years	46 (62.2)	17 (47.2)	[redacted]
≥85 years	0 (0.0)	0 (0.0)	[redacted]
Race n (%)			
White	73 (98.6)	36 (100.0)	[redacted]
Asian	1 (1.4)	0 (0.0)	[redacted]
Ethnicity n (%)			
Hispanic or Latino	1 (1.4)	0 (0.0)	[redacted]
Not Hispanic or Latino	73 (98.6)	36 (100.0)	[redacted]
Weight (kg)			
Mean (SD)	79.8 (14.0)	80.6 (16.4)	[redacted]
Median	79.0	81.4	[redacted]
Min, max	49, 116	50, 128	[redacted]
BMI (kg/m2)			
Mean (SD)	27.7 (3.8)	28.5 (6.0)	[redacted]
Median	27.5	28.3	[redacted]
Min, max	19, 35	19, 41	[redacted]
Drooling aetiology n (%)			
Parkinson's disease	53 (71.6)	26 (72.2)	[redacted]
Atypical parkinsonism	5 (6.8)	3 (8.3)	[redacted]
Stroke	14 (18.9)	6 (16.7)	[redacted]
Traumatic brain injury	2 (2.7)	1 (2.8)	[redacted]

uSFR g/m mean (SD)	0.40 (0.27)	0.38 (0.23)	[redacted]
DSFS mean (SD)	6.78 (0.90)	6.97 (1.06)	[redacted]
Injection guidance n (%)			
Ultrasound guided	41 (55.4)	18 (50)	[redacted]
Anatomical landmarks guided	33 (44.6)	18 (50)	[redacted]

BMI: body mass index; DSFS, drooling severity and frequency scale scored 2 (best) – 9 (worst); PD: Parkinson's disease; SD: standard deviation; uSFR, unstimulated salivary flow rate.

Table 6: Baseline characteristics NCT01653132[12]

	PBO first N=4	**CBTA first N=5**
Age, years (mean ± SD)	64.7 ± 4.8	70.8 ± 12.3
Sex n (%)	Male 3 (75)	Male 3 (60)
	Female 1 (25)	Female 2 (40)
Body Mass Index (mean ± SD)	28.5 ± 4.36	28 ± 8.9
DSFS (median, (IQR))	6 (5.5 - 6.25)	7 (6 - 7)
Saliva weight, grams per 5 minutes (mean ± SD)	2.73 ± 2.84	1.65 ± 1.44

DSFS, drooling severity and frequency scale scored 2 (best) – 9 (worst). IQR=inter quartile range; SD: standard deviation

In the crossover trial NCT01653132[12] one patient discontinued, to start anticholinergic treatment for tremor, and was not included in analyses. Discontinuations in the SIAXI RCT, (CS Section B.2.4.1) are shown in Table 7. Flow diagrams for participants in the SIAXI MP and EP are provided by the CS in CS Appendix L.

In the MP, AEs were cited as reason for discontinuation in one patient of each of the CBTA 100U and PBO groups, but these AEs were not considered treatment related (CS Section B.2.4.1).

In the EP, CBTA 100U group, 14 /89 (15.7%) patients discontinued treatment. AEs leading to discontinuation were experienced by eight patients, [redacted].

Table 7: Discontinuations in SIAXI MP and EP (Adapted from CS Table 8 and CS Table 9)

	MP		EP
	CBTA 100 U (N=74)	**Placebo (N=36)**	**CBTA 100 U (N=89)**
Discontinued n (%)	2 (2.7)	4 (11.1)	14 (15.7)
Reason for discontinuation* n			
Death	0	0	2
AE(s)	1	1	8
Patient withdrawal	1	3	8
Physician decision	1	1	2
Loss to follow-up	1	0	0
Lack of efficacy	0	0	1

*multiple reasons

3.2.2 Effectiveness of CBTA

Results of the SIAXI RCT were provided in CS Section B.2.6 and results of NCT01653132 were provided in CS clarification response A5.

Unstimulated salivary flow rate

The crossover trial NCT01653132 reported no significant difference between CBTA 100U and (PBO) treatment periods, in the change in saliva weight (over five minutes) at one month follow-up: mean difference -0.194 (standard deviation (SD) 0.61).[12]

At four weeks' follow-up of the SIAXI MP (CS Section B.2.6.1), there was a statistically significant (p=0.004) greater reduction in uSFR for the CBTA 100U group (LS mean change -0.13) compared with the PBO group (LS mean change -0.04) (Table 8). This difference remained statistically significant throughout the MP (Table 8). [redacted]

[redacted]

[redacted]

Table 8: uSFR (g/min) MP of SIAXI (MMRM) Table adapted from CS Section B.2.6.1 Table 11 and Figure 5 and CSR[7]

	CBTA 100 U		Placebo	
	n		**n**	
Baseline				
Mean (SD)	74	0.40 (0.27)	36	0.38 (0.23)
Week 4				
Mean (SD)	73	0.27 (0.18)	36	0.36 (0.19)
Mean change from baseline to Week 4				
Mean change (SD)	73	-0.12 (0.21)	36	-0.03 (0.21)
LS-Mean change (SE) (95% CI) [6]	73	-0.13 (0.026) (-0.18; -0.08)	36	-0.04 (0.033) (-0.11; 0.03)
LS-Mean change difference versus placebo (95% CI) [6, 7]	73	-0.09 (0.031) (-0.15; -0.03)	-	-
p-value (versus placebo)		0.004	-	-
Mean change from baseline to Week 8				
LS-Mean change (SE) (95% CI) [6]	73	-0.13 (0.026), (-0.19; -0.08)	36	-0.02 (0.033), (-0.08; 0.05)
LS-Mean change difference versus placebo (95% CI)	73	-0.12 (0.030), (-0.18; -0.06)		
p-value (versus placebo)		<0.001		
Mean change from baseline to Week 12				
LS-Mean change (SE) (95% CI) [6]	73	-0.12 (0.026), (-0.17; -0.07)	36	-0.03 (0.033), (-0.09; 0.04)
LS-Mean change difference versus placebo (95% CI)	73	-0.09 (0.031), (-0.15; -0.03)		
p-value (versus placebo)		0.004		
Mean change from baseline to Week 16				
LS-Mean change (SE) (95% CI)	73	-0.11 (0.027), (-0.17; -0.06)	36	-0.01 (0.035), (-0.08; 0.06)
LS-Mean change difference versus placebo (95% CI)	73	-0.10 (0.033), (-0.17; -0.04)		
p-value (versus placebo)		0.002		

LS-Means are from the mixed model repeated measurement (MMRM) analysis with treatment, country, gender, use of ultrasound and aetiology included as (fixed) factors and uSFR at baseline included as covariate. For MMRM visit*treatment is an interaction term and visit is a repeated factor. CI: confidence interval; LS: least squares; MP: main period; SD: standard deviation; SE: standard error; uSFR: unstimulated salivary flow rate.

Table 9: uSFR (g/min) in EP of SIAXI reproduced from CS Section B.2.6.2 Table 17

	CBTA 100 U	
	N	**Mean (SD)**
Change from study baseline in Cycle 2		
Baseline	[redacted]	[redacted]
Week 4	[redacted]	[redacted]
Week 16	[redacted]	[redacted]
Change from study baseline in Cycle 3		
Baseline	[redacted]	[redacted]
Week 4	[redacted]	[redacted]
Week 16	[redacted]	[redacted]
Change from study baseline in Cycle 4		
Baseline	[redacted]	[redacted]
Week 4	[redacted]	[redacted]
Week 16	[redacted]	[redacted]
Change from study baseline to the end of the study	[redacted]	[redacted]

EP: extension period; SD: standard deviation; uSFR: unstimulated salivary flow rate.

Patient's Global Impression of Change Scale (GICS) response rates

At week 4 of the SIAXI MP, the patient's GICS mean score for the CBTA 100U group was 1.04, and for the PBO group was 0.47 (Table 10) (CS Section B.2.6.1). The respective carer's GICS at this follow up [redacted]

By least squares means of patients' GICS, the difference between CBTA 100U and PBO groups was statistically significant at four weeks (p=0.002), however, the impact on the patient may not be substantial, as the 1.04 change for CBTA in the patients GICS is marginally above minimally improved function (i.e. a change of 1), and the change for PBO patients was 0.47[redacted]

[redacted]Table 10[redacted].

CS Section B.2.6.2 Tables 18 and 19 report patients' GICS for the EP of SIAXI. Response rates in the CBTA 100U treatment group ranged from [redacted]

Subgroup data were reported. [redacted]

Table 10: Patients' GICS MP adapted from CS Tables 12 and 13 and Figure 6 and CSR[7]

	CBTA 100 U		Placebo	
	n		n	
Week 4				
Mean score at Week 4 (SD)	73	1.04 (1.03)	36	0.47 (0.84)
LS-Mean (SE) (95% CI)	74	1.25 (0.144) (0.97; 1.53)	36	0.67 (0.186) (0.30; 1.04)
LS-Mean difference versus placebo (SE) (95% CI)	74	0.58 (0.183) (0.22; 0.94)		
LS-Mean difference p-value		0.002		
Response rate (GICS score of ≥1) Week 4 n (%)	73	53 (72.6)	36	16 (44.4)
Response rate p-value		0.006		
Week 8				
LS-Mean (SE) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
LS-Mean difference versus placebo (SE) (95% CI)	[redacted]	[redacted]		
LS-Mean difference p-value		[redacted]		

Response rate (GICS score of ≥1) Week 8 n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Response rate p-value		[redacted]		
Week 12				
LS-Mean (SE) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
LS-Mean difference versus placebo (SE) (95% CI)	[redacted]	[redacted]		
LS-Mean difference p-value		[redacted]		
Response rate (GICS score of ≥1) Week 12 n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Response rate p-value		[redacted]		
Week 16				
LS-Mean (SE) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
LS-Mean difference versus placebo (SE) (95% CI)	[redacted]	[redacted]		
LS-Mean difference p-value		[redacted]		
Response rate (GICS score of ≥1) Week 16 n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Response rate p-value		[redacted]		

Global impression of change scale (GICS) scores range from 3 (best) to -3 (worst) GICS scores were analysed via the MMRM approach. LS-Means are from model with treatment, country, gender, use of ultrasound and aetiology included as (fixed) factors and DSFS sum score at baseline included as covariate. For MMRM visit*treatment is an interaction term and visit is a repeated factor. CI: confidence interval; LS: least squares; MMRM: mixed model repeated measurement analysis; MP: main period; SD: standard deviation; SE: standard error.

Other measures of salivary flow

DSFS was measured in both CBTA trials. The crossover trial NCT01653132 reported means, whereas SIAXI reported LS-means, so the results are not directly comparable.

[redacted]

The crossover trial, NCT01653132, reported that the one month follow-up mean difference between groups in change in DSFS was non-significant -0.33 (SD 1.41, 95% CI -1.16 to 0.69).[12, 15] This was based on the combined pre- and post-crossover periods (n=9), with DSFS on CBTA 100U treatment of mean change -1.00 (SD 1.41), and on PBO mean change -0.67 (SD 0.7).[11]

The crossover trial NCT01653132 reported no significant difference between CBTA 100U and PBO treatment periods, in the change in saliva weight at one-month follow-up, mean difference: -0.194 (SD 0.61). [12, 15]

[redacted]

3.2.3 Adverse events of CBTA

The crossover trial NCT01653132 assessed AEs in nine Parkinson's disease patients.[12] During the CBTA 100U treatment period two participants reported AEs: difficulty chewing and motor control of the tongue, and viscous saliva. [12, 15] CBTA and PBO periods were compared on the UPDRS ADL (Unified Parkinson's Disease Rating Scale activities of daily life) swallowing item and no significant difference was found.[12]

In the SIAXI RCT, all patients who received study medication (CBTA or PBO) were included in the Safety Evaluation Set (SES) [CS Section B.2.4].

[redacted]

Table 11: [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	

The most commonly observed adverse reactions are shown in Table 12 as taken from the Food and Drug Administration label for CBTA.[17] The most commonly reported AEs in the CBTA 100U group were tooth extraction, dry mouth, diarrhoea and hypertension. Clinical advice to the ERG suggested that the frequency of tooth extraction was a surprising finding given the short duration and may be suggestive of a risk of dental caries, which may be a potentially serious side effect.

Table 12: SIAXI MP Adverse Reactions (≥3%) (Table reproduced from Food and Drug Administration label)[17]

Adverse Reaction	CBTA 100 Units (N = 74) (%)	Placebo (N = 36) (%)
Tooth extraction	5	0
Dry mouth	4	0
Diarrhoea	4	3
Hypertension	4	3
Fall	3	0
Bronchitis	3	0
Dysphonia	3	0
Back pain	3	0
Dry eye	3	0

In SIAXI, treatment emergent AEs and SAEs were defined as those "*with onset or worsening at or after the first injection of Xeomin or placebo up to and before the first injection of the EP or, in the case of discontinuation before the EP, up to and including 16 weeks after the first injection or the date of the last study visit, whichever was later*" (CS Section B.2.10.1). Treatment-related AEs ([redacted] were considered separately. Numbers of patients with AEs and SAEs are shown in Table 13. In the MP, 45.9% of the CBTA 100U group, and 41.7% of the

placebo group, experienced one or more AE. Of these, 8.1% and 8.3% respectively were considered treatment-related.

In the MP, none of the SAEs was considered treatment-related. In the EP, [redacted]

Changes in mROMP swallowing symptoms were considered to [redacted]

Table 13: AE summary SIAXI MP (adapted from CS Table 34 and Table 40)

	MP	MP	EP
Number of patients with at least one AE, n (%)	**CBTA 100 U (N=74)**	**Placebo (N=36)**	**CBTA 100 U (N=89)**
Any AE	34 (45.9)	15 (41.7)	[redacted]
Treatment-related AEs	6 (8.1)	3 (8.3)	[redacted]
Any AE of special interest	5 (6.8)	0 (0.0)	[redacted]
Treatment-related AE of special interest	1 (1.4)	0 (0.0)	[redacted]
Any SAE	9 (12.2)	3 (8.3)	[redacted]
Treatment-related SAEs	0 (0.0)	0 (0.0)	[redacted]
Any AE leading to discontinuation	1 (1.4)	0 (0.0)	[redacted]
Treatment-related AEs leading to discontinuation	0 (0.0)	0 (0.0)	[redacted]
Any fatal AE	0 (0.0)	0 (0.0)	[redacted]

*Neither fatal AE considered treatment-related

3.2.4 Health-related quality of life CBTA

SIAXI measured HRQoL by the EQ-5D-3L VAS (the 3-level version of the EuroQol five dimension measure of HRQoL), in the MP (Table 14) and the EP (Table 15). The mean baseline values were [redacted]

Table 14: EQ-5D-3L VAS (0-100) change from baseline SIAXI MP (table adapted from CS Table 24)

	CBTA 100 U		Placebo	
	N	Mean (SD)	N	Mean (SD)
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]

Table 15: EQ-5D-3L VAS (0-100) change from baseline SIAXI EP (table adapted from CS Table 25)

	CBTA 100 U	
	N	Mean (SD)
Cycle 2 Week 4	[redacted]	[redacted]
Cycle 3 Week 4	[redacted]	[redacted]
Cycle 4 Week 4	[redacted]	[redacted]

The SIAXI RCT also collected EQ-5D-3L data from each of the five domains and converted these to utility values as described in Section 3.4.5 of the CS. These analyses are detailed in Section 4.2.5.4 and critiqued by the ERG in Section 4.3.4. In summary the company estimate, using a latent class mixture model (LCMM), that the utility values taken directly from the SIAXI study are: 0.6397 for patients with mild or resolved sialorrhoea; 0.5974 for patients with moderate sialorrhoea; and 0.585 for patients with severe sialorrhoea.

3.3 Critique of trials identified for treatment comparison

The systematic review by the CS (CS Appendix D) identified 15 potentially relevant trials of comparators. However, none of these were considered eligible for evidence synthesis with the SIAXI trial. Reasons for excluding these studies are presented in the CS Section B.2.9 and the Tables 1 and 2 of the company's clarification response. The reasons included the heterogeneity in patient population, study design, outcome assessed. The company noted that the most important reason was the outcomes measured differed substantially in terms of assessment time-points and measurement used.

The ERG disagrees the use of an arbitrary cut-off of sample size <30 as one of the rules to exclude studies, but accepts that there was substantial heterogeneity between trials, and it was not appropriate to conduct a network meta-analysis.

3.4 Conclusions of the clinical effectiveness section

The ERG believes that no RCTs of CBTA meeting the inclusion criteria of the final scope[5] have been missed. The search for clinical evidence reflected the decision problem in the final scope.[5]

Two relevant RCTs of CBTA were identified. One of these, NCT01653132, was a small (n=9) crossover trial, that did not report pre-crossover results. No evidence synthesis was attempted with SIAXI and NCT01653132, but the ERG considered this was appropriate, and that it was reasonable to assume these data would not have substantially altered the results.

The key clinical effectiveness evidence for CBTA was based on the SIAXI trial. The MP of SIAXI was a 16-week parallel group RCT with three groups: PBO (n=36); CBTA 100U (n=74); and CBTA 75U (n=74); the 75U dose is not part of marketing application so was not considered ERG report. The EP of SIAXI followed with up to 48 weeks of CBTA 100U (n=89), or CBTA 75U (n=84). The SIAXI RCT was of good methodological quality. Fifteen RCTs of comparators were identified, but no network meta-analysis was conducted, which the ERG believes was reasonable given the heterogeneity between trials.

The population of SIAXI was considered generalisable to a UK population of Parkinson's Disease and stroke patients. In practice, more aetiologies of sialorrhoea, e.g. motor neurone disease and neurodevelopment disorders, would be eligible for treatment.

The co-primary outcomes of SIAXI were uSFR, an objective measure of salivary flow, and patients' GICS, a patient reported outcome of change. SIAXI showed a statistically significantly (p=0.004) greater reduction in uSFR for the CBTA 100U group (LS mean change -0.13) compared to the PBO group (LS mean change -0.04) at 4 weeks' follow-up of the MP. This difference remained statistically significant throughout the 16 weeks of the MP. [redacted]

The participant's GICS showed a statistically significant (p=0.002) advantage for CBTA 100U (LS-mean 1.25) over placebo (LS-mean 0.67) at 4 weeks' follow-up of the SIAXI MP. This difference remained statistically significant at p≤0.001 to week 12, and at p=0.011 at week 16 [redacted]

.

The most commonly reported adverse events (AEs) in the CBTA 100U group were tooth extraction, dry mouth, diarrhoea and hypertension. In the SIAXI MP, 45.9% of the CBTA 100U group, and 41.7% of the placebo group, experienced one or more AE. These were considered treatment-related for 8.1% of the CBTA 100U group, and 8.3% of the placebo group. None of the SAEs in the SIAXI MP were considered treatment-related. [redacted]

[redacted]

4 COST EFFECTIVENESS

4.1 Summary of the literature review of cost-effectiveness studies performed by the company

The company performed three searches in August 2018 to identify i) economic evaluations of pharmacological interventions for the treatment of people with sialorrhoea ii) health related quality of life of people with sialorrhoea and iii) health care resource and allocation.

A systematic literature search was performed on the 30th August 2018 in MEDLINE [via Ovid], MEDLINE In-Process & Other Non-Indexed Citations [via Ovid], Embase [via Ovid], HTA database [via CRD], and NHS EED [via CRD], which was only maintained to 2015. The company carried out a manual search of five conference abstracts books (American Academy of Neurology, Association of British Neurologists, European Academy of Neurology, International Congress of Parkinson's Disease and Movement Disorders and the International Society for Pharmacoeconomics and Outcomes Research Annual European and International Congresses) covering the period from 2016 to 2018.

The company performed supplementary searches in several international HTA agencies (NICE, SMC and AWMSG) and health utilities databases (The Cost-Effectiveness Analysis Registry by Tufts Medical Center, the University of Sheffield Health Utilities Database, and the EQ-5D publications database. The searches covered the period up to September 2018.

In Appendix G, full details of the search strategies were provided. The company reported full literature search strategies for the disease area sialorrhoea combined with an economic evaluation, HRQoL and cost/resource use studies filters and publication exclusion filters. The ERG considers that the searches are sufficiently comprehensive to retrieve all the eligible studies.

The literature review undertaken by the company did not identify any previous published economic evaluations relevant to the decision problem. Furthermore, the company state that no papers were identified that provided data on the utility, cost or resource use associated with patients with chronic sialorrhoea.

4.2 Summary of the company's submitted economic evaluation

Following the clarification round the company submitted a new model; the ERG will focus solely on this new model within its critique. For information, in response to the clarification questions, the company made two major structural modifications to the model and one input change: a summary of these changes is provided:

- The last observed transition matrix for each intervention was carried forward for subsequent cycles till the end of the model rather than assuming that all patients remained in their health state at 52 weeks
- The company assumed that patients could not discontinue Standard of Care (SoC) treatment whilst patients who discontinue on active treatment are assumed to be treated with SoC alone. Patients who discontinued active treatment were explicitly modelled across the three severity-based health states according to the transition probabilities for the SoC alone arm of the model. These patients were also assumed to have the same resource utilisation as patients receiving SoC alone.
- A continuity correction was applied to the transition probability matrices so that transitions between states were not set to zero, which could be observed due to low sample sizes. In any given transition probability matrix, if certain transitions were found to be absent (i.e. the probability equals zero), one patient was added to each cell of the corresponding 'from health state row'.

The company introduced two changes to the sensitivity analysis. The first change was fixing the acquisition costs of CBTA, with the second change utilising the lower and upper quartiles of NHS reference costs to calculate confidence intervals and standard deviation in order to estimate uncertainty.

4.2.1 Population

The population included in the company's health economic analysis reflects adult patients with chronic, moderate or severe, sialorrhoea. The analysed patient population was not restricted to patients with chronic sialorrhoea with a specific aetiology, as the company states that the mechanism of action of CBTA is independent of the cause of sialorrhoea. The cohort of patients modelled were assumed to be 65.2 years of age, 70.7% male, and with 54.55% in the severe sialorrhoea state, 45.45% in the moderate sialorrhoea state and 0.00% in the mild/resolved sialorrhoea state (as later defined) in accordance with data observed in the SIAXI study.

4.2.2 Interventions and comparators

In the SIAXI trial, CBTA (at a dose of 100 U) was administered as four injections into parotid and submandibular salivary glands every 16 weeks. CBTA was modelled in combination with SoC, which represents basic non-pharmacological sialorrhoea management. Non-pharmacological clinical management may contain: practical aids, (such as bibs) speech, language, and occupational therapy, according to the clinical experts who advised the company.

Comparators included systemic anticholinergic therapies, which according to feedback received by the company from clinical experts represent the active pharmacological therapy received by the majority of patients in the UK. Oral glycopyrronium bromide (administered as tablets or solution) was stated to be one of the most commonly tried anticholinergic therapies for the treatment of sialorrhoea in UK clinical practice. Active therapy is prescribed alongside SoC, thus glycopyrronium bromide plus SoC formed the principal comparator in the model. Other active anticholinergic therapies such as transdermal hyoscine hydrobromide and sublingual atropine sulfate may be used in some patients and these were included as comparators within scenario analyses.

As per the NICE final scope,[5] for patients where anticholinergic therapy is unsuitable or inefficient, SoC alone was included as a comparator in the model.

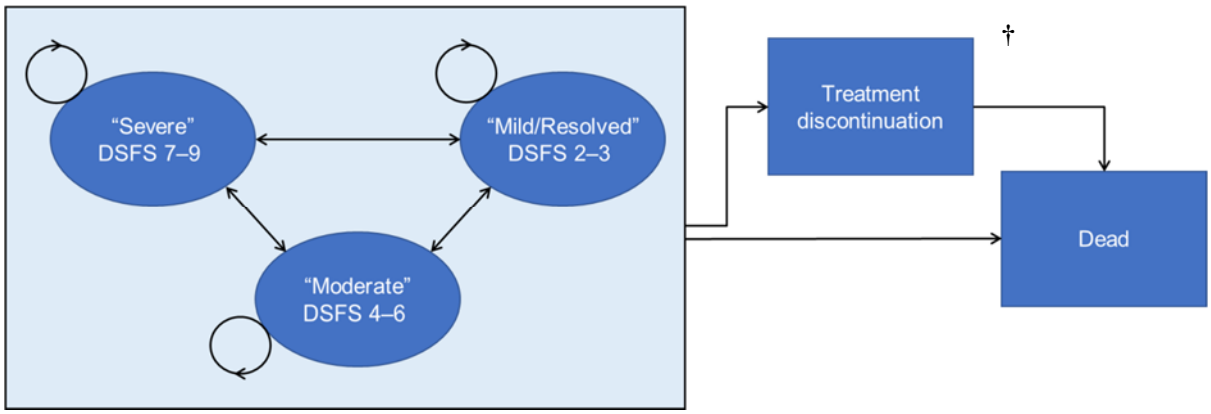
4.2.3 Perspective, time horizon and discounting

The base case model adopts an NHS and Personal Social Services (PSS) perspective. The time horizon of the model in the base case is ten years although other values were included in scenario analyses. Both costs and QALYs were discounted at 3.5% per annum as recommended by NICE.[4]

4.2.4 Model structure

As part of its submission to NICE, the company submitted a fully executable health economic model programmed in Microsoft Excel®. The submitted model adopts a cohort-level Markov state transition approach which consists of seven health states: (1) mild/resolved sialorrhoea; (2) moderate sialorrhoea; (3) severe sialorrhoea; (4-6) Treatment discontinuation (mild/resolved; moderate; severe); and (7) dead. The company's diagram of the model structure is provided in Figure 3. Cycle lengths were set to 16 weeks to coincide with the timing of CBTA injections.

The overall DSFS score was used to define the three sialorrhoea severity-based health states. The company suggests that DSFS was deemed the most clinically relevant measure of sialorrhoea disease severity based on feedback from clinicians. The DSFS consists of two subscales; a 5-point Likert scale for classifying drooling severity (where 5 indicates profuse drooling) and a 4-point Likert scale for classifying drooling frequency (where 4 is constant drooling). Both subscale scores are summed to give an overall score ranging from 2 to 9. The overall score was then used to categorize sialorrhoea severity into three categories, as follows: severe sialorrhoea (DSFS 7-9), moderate sialorrhoea (DSFS 4-6), and mild/resolved sialorrhoea (DSFS 2-3). Clinical advice to the ERG suggested that these groupings were appropriate, although one clinician believed that a DSFS score of four could be grouped as mild sialorrhoea. This was not a change that could be made by the ERG whilst assuming that patients on SoC could not become mild / resolved and was thus not enacted.



† Patients who discontinued active treatment continued to be explicitly modelled across the three severity-based health states

Figure 3: The company's model structure

Baseline health state distributions were based on baseline DSFS scores reported in the SIAXI trial.[8] Transitions were allowed between any of the three sialorrhoea severity-based health states.

Patients could transition from any of the three severity-related health state to one of three health states (one for each severity level of sialorrhoea) which denote that treatment has been discontinued.

Patients in any of the four alive health states could transition to the absorbing death health state, with a transition probability that was deemed equal across all health states. General mortality rates as reported in the ONS National Life Tables for the years 2015 – 2017 were applied.[18] No excess mortality was assigned to the underlying aetiology of sialorrhoea.

4.2.5 Evidence used to inform the company's model parameters

4.2.5.1 Transitions between sialorrhoea severity-based health states

Patient-level DSFS data from the SIAXI trial was used to inform the transition probabilities between the three sialorrhoea severity-based health states. Data were available relating to the first four injection cycles for CBTA plus SoC (CBTA arm), and for the first cycle for SoC, where one cycle is equivalent to 16 weeks. The DSFS score was assessed four weeks after each treatment, and were utilised to derive transition matrices between sialorrhoea severity states. There was a discrepancy between the time cycles used in the model, which started at each potential CBTA injection (week 0, week 16, week 32 and week 48) and the assessment of DSFS score (week 4, week 20, week 36 and week 52). The company assumed that the observed transitions between week 0 and week 4, would be generalisable to the transitions between week 0 and week 16; and that the observed transitions between week 4 and 20 would be generalisable to transitions between week 16 and week 32, and so on.

Following its response to clarification question B10, the company assumed that the last observed transition matrix would be carried forward (i.e. the week 36 to week 52 matrix for CBTA and the baseline to week 4 matrix for SoC were used to inform transitions at all the following model cycles).[15]

Due to the limitations encountered in establishing a relative treatment effect of glycopyrronium bromide the company assumed that its efficacy is 75% that of CBTA. This assumption was based on an analysis conducted by NICE for the development of the clinical guideline of cerebral palsy in under 25s,[3] where glycopyrronium bromide and CBTA improved the drooling scores by 3 and 4 points respectively. To implement this, glycopyrronium bromide used the same transition matrices of CBTA but with the probabilities of health state improvements to be 75% of the CBTA values with the remaining 25% staying in the same health state if they were estimated to improve by one state on CBTA, or improving one health state if CBTA was assumed to generate a 2-step improvement. To acknowledge the uncertainty within this assumption the company performed a scenario analysis where the efficacy of glycopyrronium bromide was assumed to be equal to that of CBTA.

4.2.5.2 Treatment discontinuation

Following discontinuation from CBTA or glycopyrronium bromide, a patient was assumed to stay within the same severity category in that cycle and to subsequently receive SoC. In future cycles the patient would follow the transition probabilities and resource use associated with SOC. For all active interventions it was assumed that discontinuation rates were independent of patients' severity status. The company assumed that no patient discontinues SoC.

Discontinuation rates on CBTA plus SoC were informed by the SIAXI trial. Accordingly, the discontinuation rate observed during the maintenance phase of the SIAXI trial (2.7%) was applied for the first model cycle, whereas all subsequent model cycles used the mean discontinuation rate observed during the extension phase of the SIAXI trial ([redacted]).

For glycopyrronium bromide the company sought feedback from UK clinical experts, who indicated that approximately 50% of patients on glycopyrronium bromide would discontinue in the first 16 weeks of treatment. This relatively high proportion was assumed to be attributed mainly to adverse events which would occur within the first 16 weeks. In subsequent model cycles, discontinuation rate for glycopyrronium bromide was assumed to be the same as CBTA ([redacted]). The company performed scenario analyses where the discontinuation rate associated with glycopyrronium bromide in the first 16 weeks was reduced to 25%. Clinical advice provided to the ERG stated that the discontinuation rate on glycopyrronium in the first 16 weeks was likely to lie between 25 and 50%.

Clinician feedback to the company suggested that there would be no limit on the duration of treatment for patients who are either on glycopyrronium bromide or CBTA, hence no stopping rules were explored in the base case. Within its response to clarification question B2, the company explored stopping the active treatment at three separate model cycles (cycles 2, 3, or 4), where patients, who had severe sialorrhoea, in that cycle only, were presumed to discontinue treatment.[15]

4.2.5.3 Mortality

The model referenced general population mortality to inform mortality rates used in the model. These rates were based on the ONS National Life Tables in England and Wales for the years 2015 – 2017[18] and were assumed to apply to all patients irrespective of treatment. No excess mortality was associated with sialorrhoea, or with underlying aetiology. Whilst clinical advice to the company suggested that patients with sialorrhoea have an increased mortality risk compared with the general population the company claimed that this relative increase is unknown and difficult to determine, although the company undertook a scenario analysis using a standardised mortality ratio (SMR) of 1.82 based on a value for patients with Parkinson's disease.[19] In its response to clarification question A10, the company conducted a rapid literature review of SMR data for Parkinson's disease and stroke. SMR for Parkinson's disease ranged from 1.39 to 3.6, whereas it registered a wider range of values for stroke (1.46 – 6.94). The company presented a series of scenario analyses using the upper and lower SMR value for each condition.[15]

4.2.5.4 Health related quality of life

HRQoL data were collected in the SIAXI trial using the EQ-5D-3L, and the results were presented in Section B.2.6.3 of the CS. SLR for relevant utility studies of adults with chronic sialorrhoea did not identify any studies reporting utility data for the relevant population.

There were significant improvements in efficacy outcome measures used (uSFR, GICS and DSFS) as a result of CBTA treatment, however, [redacted].

The CS notes that it has been shown that EQ-5D may be insensitive to changes in disease severity in a number of disorders, particularly those that are neither painful nor life-threatening, and this may apply to sialorrhoea. Patients experiencing sialorrhoea have normally a variety of underlying aetiologies such as Parkinson's disease or stroke. The value of EQ-5D improvements associated with sialorrhoea severity may be obscured by the HRQoL impact of the underlying condition. As a result, the CS states that EQ-5D may not be able to capture health gains associated with improvements in sialorrhoea severity state.

In the clarification process, question A1, the ERG asked the company to provide more detail on why the EQ-5D may be insensitive to improvements in the severity of sialorrhoea.[15] The company provided data on the percentage of patients with a score of 2 (some problems) for each domain at baseline in the SIAXI trial (mobility: [redacted]%; self-care: [redacted]%; usual activities: [redacted]%; pain: [redacted]%; anxiety/depression: [redacted]%); the breakdown of the remaining patients between scores of 1 and 3 were not provided. The company stated that given the impact of trial patients' severe underlying conditions on HRQoL, it is highly unlikely that many of these patients would be able to rate that there was "no problem" for many of the domains. The company claimed that whilst improvements in sialorrhoea severity are associated with a positive impact on HRQoL, these could be negated and not recognised by the EQ-5D-3L scoring system due to the impact of the underlying condition.

The CS used two methods for estimating mean health state utilities. The first method was based on exploring different regression models to predict EQ-5D utility values given patient-level DSFS sum scores from the SIAXI trial. Patient-level EQ-5D index scores from the SIAXI trial exhibited a multimodal distribution, and linear regression models were deemed inappropriate to handle this type of data, so latent class mixed models (LCMM) were explored. Class membership of a given LCMM was modelled via multinomial regression, and a maximum likelihood estimation method was used estimate the parameters of all LCMMs assuming that dropouts were missing at random. All models were fitted in R using the LCMM package.

The best fitting LCMM was determined using the Bayesian Information Criterion (BIC). The mean utility for each level of the DSFS sum score was estimated using a weighted average across latent classes. The mean utility for mild/resolved, moderate and severe states was estimated by averaging the mean utility for the DSFS scores 2-3 for mild/resolved, 4-6 for moderate and 7-9 for severe. Further details of the model selection and estimated parameters for the best fitting model can be found in the response to clarification questions A12 and A13.

The company's preferred LCMM (three latent classes, class-specific mean trends, and no variable specified to inform class membership) estimated the mean utility values each health state as: mild/resolved (0.6397); moderate (0.5974); and severe (0.5854). The difference between severe and mild/resolved state was 0.0543, and between moderate and mild/resolved was 0.0423. The company stated that these values do not reflect the real differences in HRQoL between the different severity levels. As a result, the company proposed a second method for estimating the mean utility values of each health states.

The second method relied on a hypothetical set of utility values of different drooling severity health state reported in a cost-effectiveness analysis conducted for the NG62 guidelines,[3] because no relevant utility data were identified in the SLR. The hypothetical utility values introduce a fixed disutility decrement of 0.025 for every unit increase in the NG62 drooling severity score, which results in a utility difference of 0.2 between the least drooling health states (0.500) and most severe drooling health states (0.300) which is significantly larger than the 0.0543 estimated through the LCMM. NG62 states that the relative utility value of no drooling to profuse drooling (0.50 vs 0.30) was similar to the ratio of physical health summary scores reported in Chang *et al*.[20] (31.97 vs 16.29) which investigated HRQoL in 47 children with cerebral palsy. The ERG comments that both the NG62 and Chang *et al*. documents focus on much younger patients than those in SIAXI, and that these patients have different underlying diseases than patients recruited to SIAXI. Furthermore, these data may be confounded due to the relationship between the underlying condition and utility and the relationship between the underlying condition and severity of sialorrhoea, as measured by drooling states. As such, changing the severity of the sialorrhoea, in terms of scores such as the DSFS, would not necessarily increase the utility to the level of a patient with a less severe underlying condition as the more severe underlying condition would still be present.

The NG62 drooling severity score and DSFS sum score recorded in SIAXI are two different scoring scales. The DSFS sum score scale has a range from 2-9 with the frequency component score range from 1-4 and the severity score range from 1-5 (Table 50 of the CS). The NG62 drooling severity scale has a range from 1-9. The company matched DSFS sum score to the NG62 drooling score based on the health state descriptions of both scales as detailed in Table 51 of the CS. After matching, a simple linear regression was used to estimate the utility for each DSFS sum score (Figure 11 in the CS). The ERG notes that the matching only covered DSFS sum score 3-8 instead of the original range 2-9. The derived utility values of the corresponding DSFS sum scores were then averaged to get the mean utility value for each sialorrhoea severity health state. For example, the derived utility values for DSFS sum scores of 2 and 3 were simply averaged to get the mean health state utility value of mild/resolved sialorrhoea. The estimated mean utility for the three sialorrhoea severity health states is presented in Table 16, which also presents the mean utility estimated using LCMM.

Table 16: Derived utility values using the NG62 guidelines and latent class mixed model

	LCMM	NG62-derived values
Resolved / Mild	0.6397	0.5346
Moderate	0.5974	0.4283
Severe	0.5854	0.3008

The company states that based on the clinicians' feedback, the hypothetical utility values from the NG62 guidelines were deemed more clinically plausible compared to the estimates derived from the SIAXI

trial via the LCMM. Therefore, the utility values derived using the NG62 guidelines were used within the model base case analysis.

The company highlighted the uncertainty surrounding the adoption of the hypothetical model reported at NG62 guidelines to derive the model utility values. Therefore, they conducted a threshold analysis to identify the minimum difference required between the mild/resolved health state and the severe one to ensure CBTA being a cost-effective use of NHS resources versus SoC alone. Results indicate that this difference has to be more than 0.0746 in order for CBTA to have a cost per QALY compared with SoC of £30,000. The company claims that utility difference in clinical practice is much greater than this value despite this being greater than the EQ-5D increase estimated by the company using SIAXI data.

The frequency of AEs was similar in the SIAXI trial between CBTA treatment group and the placebo group. Hence, it was assumed that both CBTA and placebo treatment groups have the same safety profile. In addition, conducting a robust ITC between CBTA and glycopyrronium bromide in terms of safety and efficacy was not feasible. Therefore, no disutilities associated with AE were considered in the model.

4.2.5.5 Resource use and costs

The costs and resource use included in the base case model comprised: drug acquisition costs; drug administration costs; and health state related costs due to sialorrhoea management.

4.2.5.5.1 Drug acquisition costs

The cost of CBTA is £129.90 per the 100 U powder for injection, as per the online BNF.[21] This cost was considered once every model cycle where patients receive one CBTA injection each cycle.

The company sought feedback from clinicians regarding glycopyrronium bromide posology, and found that it can be administered either as tablets or in oral solution. Therefore, it was assumed that patients have equal chance of taking any of the two preparations. Feedback also indicated that the dosing regimen of glycopyrronium bromide might range between 0.3-1.5 mg three times daily. Therefore, the dose was modelled to be 1.0 mg three times daily as per a clinical trial reporting the same dosing schedule [22] and recommendations in the SPC of glycopyrronium bromide in the treatment of severe sialorrhoea in children and adolescents.[23] Acquisition costs of the two oral preparations of glycopyrronium bromide were referenced from online BNF for children [24], and were equivalent to £180.00 per 30 tablets (strength of each if 1.0 mg) and £91.00 per 150 ml oral solution (where each 5 ml contains 1.0 mg of glycopyrronium bromide). The following equation was used to calculate the acquisition cost of glycopyrronium bromide per model cycle:

$$\text{Acquisition cost of glycopyrronium bromide/cycle} = \left(0.5 * \frac{£180}{30} + 0.5 * \frac{£91}{30}\right) * 3\ times * 7\ days * 16\ weeks$$

4.2.5.5.2 Drug administration costs

Administration costs of a CBTA injection were considered and were obtained from NHS reference costs 2017-2018.[25] These costs were assumed to consist of an outpatient consultation [consultant led non-admitted face-to-face attendance, follow-up of a neurology service (currency code: WF01C)] for all patients plus an outpatient ultrasound scan [with duration of less than 20 minutes, without contrast (currency code: RD40Z)] for 56.4% of the patients. This proportion was based on the proportion of patients receiving a CBTA injection using ultrasound guidance in the SIAXI trial. Therefore, total administration costs of CBTA injection per cycle were valued at £133.51. The ERG noted that the actual value used for the outpatient consultation was non-face-to-face, using a face-to-face value would increase the cost of an outpatient appointment by £45.05, to £178.56, when using currency code: WF01A.

Administration costs were not included for either glycopyrronium bromide or the other anticholinergic therapies used in the scenario analysis because they are administered orally.

4.2.5.5.3 Sialorrhoea management costs

As discussed in Section 4.2.2, SoC represents the basic non-pharmacological sialorrhoea management, which may include speech, language and occupational therapy consultations. The consultations were assumed to vary in frequency according to sialorrhoea severity. The company assumes one speech pathology and one occupational therapy consultations for patients with 'severe' sialorrhoea per 16-week cycle, whereas patients with 'moderate' sialorrhoea were assumed to require one speech pathology or occupational therapy consultation. No sessions were assigned to patients in 'mild/resolved' health state. The company's model does not include resource use for treating the underlying condition which is assumed equal for all patients.

NHS reference costs 2017-2018 were used to obtain the costs of a speech pathology consultation and an occupational therapy consultations (£95.52 and £81.31 respectively).[25] It is unclear whether these consultations are solely related to sialorrhoea, or whether these are aimed at providing benefit related to the patient's underlying condition.

Contrary to the utility values, management costs were varied in the probabilistic sensitivity analysis without constraints on the ranking, which in a few probabilistic iterations, led to the costs associated with severe sialorrhoea being lower than that associated with moderate sialorrhoea.

4.2.6 Model validation and face validity check

The company state that they sought inputs from expert clinicians throughout the development stages of the model to ensure relevance to UK clinical practice. Expert guidance was used to inform choice of comparators, validate input and assumptions, discontinuation rates for the modelled technologies, and health state resource use.

4.2.7 Cost effectiveness results

Table 17 shows the results of the company's base case analysis for both the deterministic analysis and the PSA analysis after incorporating changes that were made during the clarification process. The PSA results are based on an ERG run using 1,000 iterations. Based on the probabilistic version of the model, CBTA plus SoC is expected to generate 0.35 additional QALYs at an additional cost of £3,279, compared with SoC alone. The corresponding ICER is £9,394 per QALY gained. The deterministic version of the company's model produces a similar ICER of £9,583 per QALY gained.

Compared to glycopyrronium bromide plus SoC, CBTA plus SoC is predicted to generate 0.2 additional QALYs at cost savings of £9,431. These figures were also in line with the deterministic version of the model. Figure 4 shows the cost-effectiveness acceptability curve (CEAC) produced by the ERG when running the company's base case, and Figure 5 presents the Markov trace graphs during the model's first 10 years.

Table 17: Company's base case results (adapted from modified base case results presented in responses to clarification questions)

Treatment	Total QALYs	Total Costs	ICER (£ per QALY gained)
Deterministic			
SoC alone	3.20	£3,010	-
CBTA + SoC	3.52	£6,103	£9,583
Glyc Br + SoC	3.34	£14,966	Dominated
PSA (run by the Evidence Review Group)			
SoC alone	3.08	£2,801	-
CBTA + SoC	3.43	£6,079	£9,394
Glyc Br + SoC	3.23	£15,510	Dominated

CBTA, Clostridium botulinum toxin A; Glyc Br, Glycopyrronium Bromide; ICER, incremental cost-effectiveness ratio; MAICER, maximum acceptable incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, Standard of Care

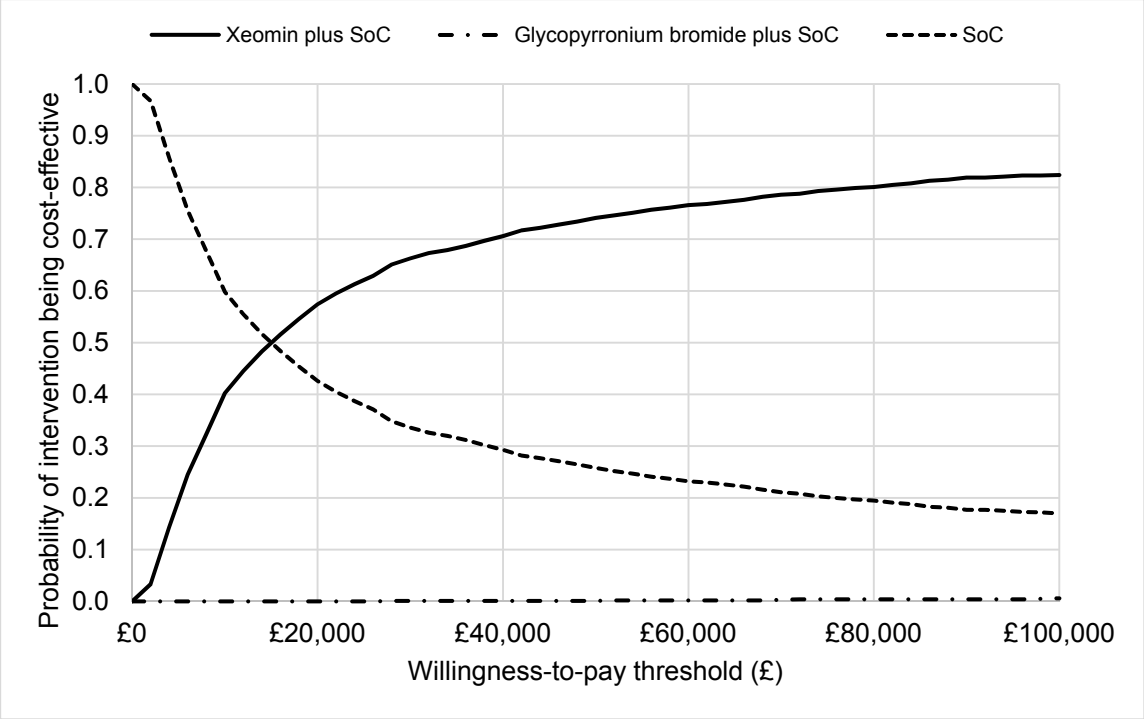


Figure 4: **Company's base case cost–effectiveness acceptability curve (adapted from modified base case results presented in responses to clarification questions)**

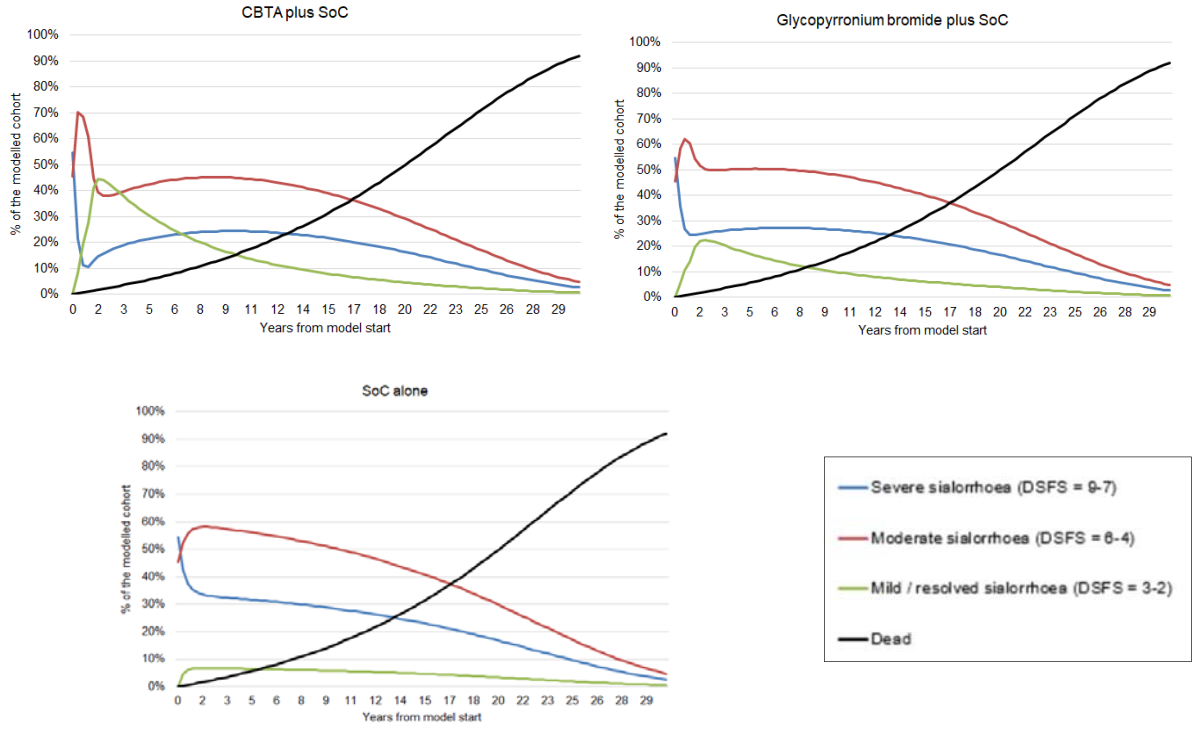


Figure 5: **Company's base case Markov trace graphs (adapted from modified base case results presented in responses to clarification questions)**

4.2.8 Sensitivity analyses

The company conducted a range of sensitivity analyses, which included: (1) a tornado diagram presenting the impact of changing parameters from their upper and lower limits; and (2) a range of scenario analyses, which included the effects of alternative assumptions and data on the results.

4.2.8.1 Tornado diagrams

The company's tornado diagrams are presented in Figures 4 and 5 of its response to clarification questions.[15] These show the ten most influential parameters in terms of impact on ICER value. Within the tornado diagrams, the following parameters were varied between the upper and lower bounds of the 95% CIs of each parameter: starting age, CBTA administration costs, sialorrhoea severity-related health state management costs, and discontinuation rates of CBTA and of glycopyrronium bromide (from cycle 2 onwards). The remaining parameters were varied between 20% of their mean values, and included: gender split, SMR, glycopyrronium acquisition costs, and discontinuation rate of glycopyrronium bromide throughout the first model cycle. The mean health state utility values were varied by 20%, with the logical ranking of the health states preserved.

The ERG noted that the company did not incorporate the uncertainty of glycopyrronium bromide's relative efficacy in their one-way sensitivity analysis. Therefore, the ERG comments that these changes may not represent the full uncertainty in the parameter values.

The tornado diagrams presented by the company reported the change in base case ICER, which was not believed to be the easiest metric to interpret. Accordingly the ERG reported these values in terms of net monetary benefit (NMB) [26] assuming a cost per QALY gained threshold of £20,000 and £30,000, and produced Figure 6 and Figure 7 for CBTA + SoC versus glycopyrronium bromide + SoC and CBTA + SoC versus SoC alone respectively. Incremental NMB measures the value of an intervention in monetary terms compared to another intervention with a positive value indicating that an intervention is more cost-effective than the comparator at the chosen threshold.

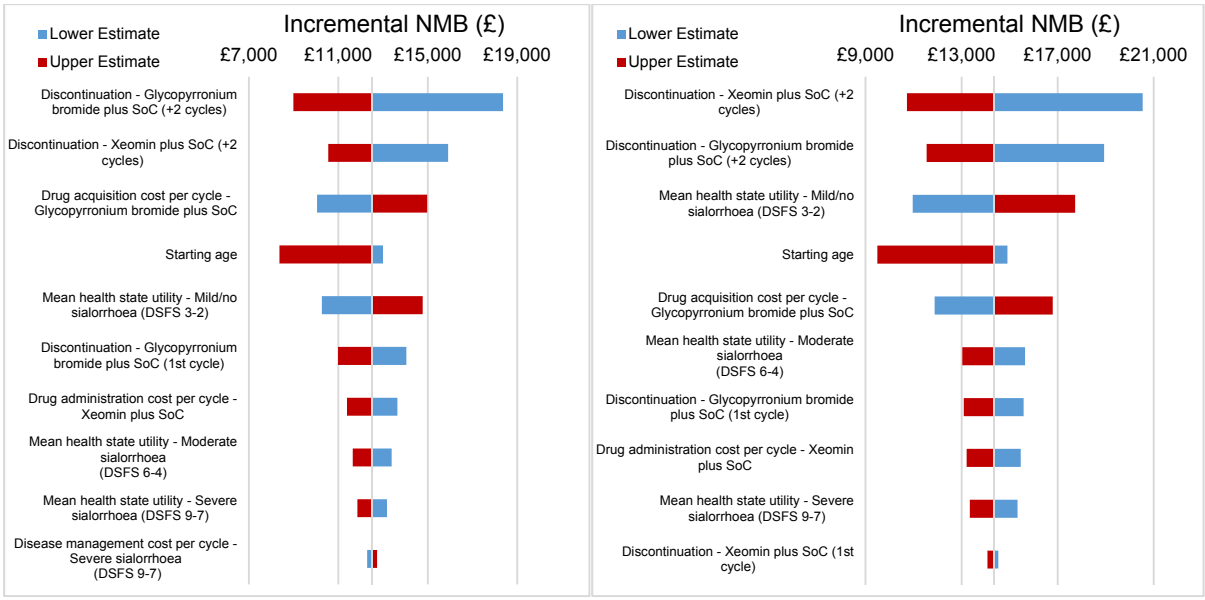


Figure 6: CBTA plus SoC vs. glycopyrronium bromide plus SoC tornado plot with NMB calculated at (a) £20,000/QALY (on the left) (b) £30,000/QALY (on the right)

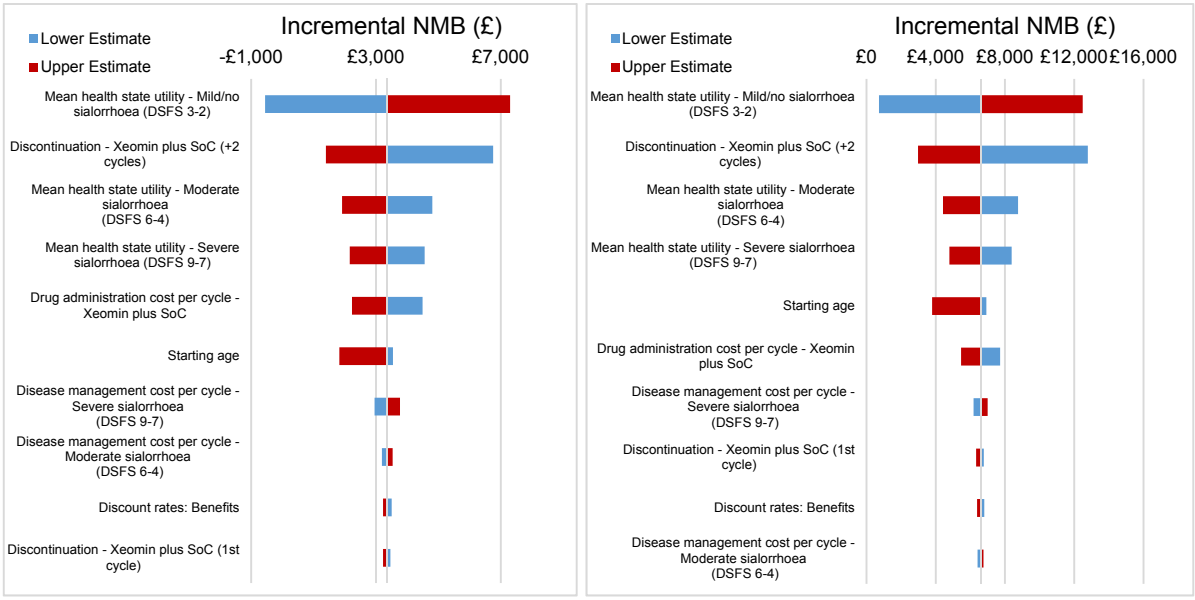


Figure 7: CBTA plus SoC vs. SoC tornado plot with NMB calculated at (a) £20,000/QALY (on the left) (b) £30,000/QALY (on the right)

4.2.8.2 Scenario and subgroup analyses

The company undertook several scenario analyses, which are presented in Tables 61 to 68 of the CS.[1] They were not all rerun following the clarification process, which the ERG believed was appropriate with the exception of omitting the analyses using the utility values estimated by LCMM. In its response to the clarification questions (Table 6), the company undertook scenario analyses using alternative SMRs, and added scenarios of applying a stopping rule of active treatment administration to patients whose sialorrhoea remained severe at specific model cycles (Table 19 of the clarification response).[15]

Generally, most scenarios produced ICERs that were similar to the base case value. The only scenario that gave a relatively high ICER was using the LCMM analysis of SIAXI study data to estimate health state utility values which resulted in a cost per QALY gained of £32,793 for CBTA + SOC compared with SOC. The majority of scenarios comparing CBTA + SoC to glycopyrronium bromide + SoC resulted in CBTA being dominant; the exceptions were when the discontinuation rates of glycopyrronium bromide and SOC were set to 50% or greater in all model cycles, which resulted in the CBTA + SOC arm costing more but provided more QALYs.

In response to clarification question B1 the company presented results separately for patients with moderate and severe sialorrhoea. These are provided in Table 18.

Table 18: Subgroup analysis by sialorrhoea severity

Treatment	Total QALYs	Total Costs	ICER (£ per QALY gained)
100% of patients enter the model in the severe health state			
SoC alone	3.18	£3,070	-
CBTA + SoC	3.51	£6,135	£9,162
Glyc Br + SoC	3.32	£15,020	Dominated
100% of patients enter the model in the moderate health state			
SoC alone	3.23	£2,939	-
CBTA + SoC	3.54	£6,064	£10,130
Glyc Br + SoC	3.37	£14,900	Dominated

4.3 Critique of company's submitted economic evaluation by the ERG

This section presents a critical appraisal of the health economic analyses presented within the CS. Section 5.3.1 details the methods used by the ERG to interrogate and critically appraise the company's submitted health economic analyses. Section 5.3.2 discusses the extent to which the company's analysis adheres to the NICE reference case. Section 5.3.3 presents a detailed critique of the main issues and concerns underlying the company's analysis.

4.3.1 Methods for reviewing the company's economic evaluation and health economic model

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic evaluation and the underlying health economic model upon which this was based. These included:

- Scrutiny of the company's model and discussion of issues identified amongst the members of the ERG.

- Examination of the correspondence between the description of the model reported within the CS and the company's executable model.
- Rerunning the DSA and PSA presented within the CS.
- Where possible, checking the parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

4.3.2 Adherence of the company to the NICE reference case

The company's economic evaluation is generally in line with the NICE reference case, details of which are given in Table 19.

Table 19: Adherence of the company's model to the NICE reference case

Element	Reference case	ERG comments
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's economic evaluation takes the form of a cost-utility analysis. The results of the analysis are presented in terms of cost per QALY gained for CBTA versus the two other comparators.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The company's model adopts a 10-year time horizon. By this point, over 66% had discontinued treatment on CBTA, and 15% were dead. The company explored different time horizons and standardised mortality rates in the scenario analyses.
Synthesis of evidence on health effects	Based on trial outcome data and systematic review	Health outcomes are modelled using the data collected in the SIAXI randomised controlled trial. It is implicitly assumed that the SIAXI trial is generalisable to UK clinical practice.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Main method used in base case analysis derived utility values from a hypothetical set of values reported in NG62 guidelines. Also, HRQoL estimates for the different severity levels of sialorrhoea were derived from EQ-5D-3L data collected in the SIAXI study.

Source of data for measurement of health-related quality of life	NG62 guidelines for the main method, and reported directly by patients and/or carers for the alternative method	The ERG had concerns with the company's approach as it used hypothetical values estimated for a different disease, and for patients who were significantly younger in preference to EQ-5D data collected within SIAXI.
Source of preference data for valuation of changes in HRQoL	EQ-5D data collected in the SIAXI trial were converted to utility values using the UK value set	The ERG had no concerns with the company's approach; however, these data were not included in the company's base case which may not adhere to the reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gained
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	Resource components included in the company's model reflect those relevant to the NHS and PSS. NHS reference costs 2017/18 were not inflated
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects are discounted at a rate of 3.5% per annum.

4.3.3 ERG Critique of the modelling performed by the company

4.3.3.1 Model verification

The ERG checked and verified the implementation of the model and the methods for generating results. During this process, the ERG identified two minor implementation errors, which were addressed by the company in their clarification response to question B6. The implemented model appears to be generally in line with its description within the CS. Individual patient-level data related to changes in DSFS scores were provided by the company and used directly in the model allowing the ERG to verify the construction of the used transition probability matrices.

4.3.3.2 Correspondence of the model inputs and the original sources of parameter values

The ERG found that some NHS reference costs had minor differences from the values reported in the CS. However, the ERG is satisfied that these discrepancies will not significantly affect the ICERs and did not alter these parameter values. All other parameters corresponded with their original source values.

4.3.4 The main issues identified by the critical appraisal

Generally, the model was well implemented and the company provided reasonable responses to the ERG clarification questions. However, the ERG identified issues within the model, some of which were identified after the clarification questions. These points are summarised in Box 1 with further details subsequently provided.

Box 1: Summary of the main issues identified within the company's health economic model

A summary of identified concerns within the company's health economic model:

1) The source of health-related utility data
2) Administration costs associated with the CBTA injections and uncertainty in the costs of administration of CBTA and of disease management
3) The implementation of discontinuation of active treatment within the model due to poor response
4) The modelling approach for patients with mild sialorrhoea who discontinue active treatment
5) The implementation of the continuity correction in the transition probability matrices
6) The patient population SMR value
7) The proportion of patients requiring ultrasound scans when receiving CBTA
8) The variance of EQ-5D mean utility values
9) The acquisition costs of glycopyrronium bromide
10) Resource use associated with different severity levels of sialorrhoea

(1) Concerns regarding source of health-related utility data

The company chose to implement the NG62 hypothetical set of utility values as its preferred approach to estimate the utility scores of the different sialorrhoea severity-related health states. As indicated in Section 4.2.5.4, the company attributed its deviation from using the EQ-5D utility data collected from the SIAXI trial within its model due to the perceived insensitivity of EQ-5D-3L to capture improvement in sialorrhoea symptoms. The company highlighted that an improvement in sialorrhoea severity state has a positive impact on patient HRQoL but that this was not captured in the SIAXI trial EQ-5D results

as "*the value of these improvements may be obscured by the HRQoL impact of the underlying condition and may not ultimately be recognised in terms of the EQ-5D-3L scoring system*".

The ERG had concerns about this approach and its relevance to the decision problem due to several reasons. In the NG62 guideline cost-effectiveness model, the disutility value applied per unit increase in drooling score was set to an arbitrary value of 0.025, and the population was strikingly different being for patients aged under 25 years with cerebral palsy, compared with a population of predominantly Parkinson's disease and stroke approximately aged 65 years. As such, the ERG believes that the use of utility data from NG62 decision problem should not take primacy over the EQ-5D data collected within the SIAXI trial given that the NICE guide to the methods of technology appraisal states that the EQ-5D is the preferred measure of HRQoL.[4] The guide also states that in cases where the EQ-5D is judged to be inappropriate, qualitative empirical evidence should be provided on its lack of content validity. However, the ERG is not convinced that this is the case with sialorrhoea. Whilst some of the reasons put forward by the company in response to clarification question A1, and detailed in Section 4.2.5.4, may be plausible, it may also be the case that the EQ-5D-3L is picking up accurately a small utility gain associated with improved sialorrhoea symptoms. The ERG also comments that the average utility for a 65-year-old is approximately 0.81,[27] and that the use of the NG62 derived data would imply that the impact of stroke or Parkinson's disease without, or with mild sialorrhoea, would be a reduction in utility of 0.28 (0.81 – 0.53 (see Table 16)). If the patient had severe sialorrhoea this would result in an additional reduction of 0.23 (see Table 16). The ERG is not convinced that severe sialorrhoea would have a similar impact on utility as the underlying condition that is causing the sialorrhoea.

Potential reasons to believe that the gain may be small include the absolute changes in the GICS scores for patients. Whilst the GICS score data observed in the SIAXI trial showed a statistically significant improvement in the CBTA 100U group compared with the placebo group at week 4, and at weeks 8, 12 and 16, of the MP this may not be clinically important. The absolute score for the CBTA 100U group at week 4 was 1.25, indicating slightly greater than minimally improved function and the difference in score compared with PBO was 0.58, which may not be large enough to have a meaningful change in function. Similar conclusions relating to GICS scores can be drawn at weeks 8, 12 and 16. Within the EP the absolute GICS score [redacted]

The ERG believes that the observed EQ-5D-3L data in SIAXI (i.e. small gain in mean utility across sialorrhoea severity health states) are coherent with the observed patient's GICS scores. Furthermore, there are a considerable proportion of patients with a domain score of either 1 or 3 (this split was not

provided by the company in the clarification response). For those patients who have a domain score of 1 then the impact of the drooling is not seen to impact on the patient, meaning that there could not be an improvement. Currently it is unclear which reason for the small utility change between severe drooling and resolved / mild drooling is correct, and given the guidance provided by NICE the ERG believes that the base case should use the EQ-5D data collected in the trial, and that alternative values should be reserved for scenario analyses.

The company referenced Hernández et al. (2012[28]) for its use of LCMM to model the utility data collected in the SIAXI trail. The ERG notes that Hernández et al. (2012[28]) recommended using the mixture models for the latent classes to deal with the distributional features in the EQ-5D data (for example the multimodal and bounded between -0.594 and 1 when using the UK tariff). However, the "lcmm" package does not incorporate mixture models for the latent classes and hence does not guarantee that the predicted utility would be bounded.

The ERG investigated the use of LCMMs without mixture models and was satisfied that none of the predicted utility values were outside of the bounds of the UK tariff. Hence the ERG believes the company's approach of using LCMM was reasonable in this case. The mixed effects modelling approach takes into account both within and between patient variability in the utility and trends in utility change over time, which is the appropriate method to use for repeated measure data. Having a latent class component in the model also allows for identifying unmeasured class membership among patients and having different relationships between the utility and health states in these "latent classes".

However, the ERG preferred an alternative method (detailed in Section 4.4.1) to that of the company to derive of the mean utility for the three sialorrhoea severity health states. The company's model used the raw DSFS sum scores and obtained the mean utility for the sialorrhoea severity health states by averaging the estimated utilities among DSFS sum scores according to the health state grouping system. This approach assigns equal weights to each level of the DSFS sum scores within a category. However, we would not expect each level of the DSFS sum scores would have equal number of patients.

The ERG also notes that the 'lcmm' package in R calculated BIC using the number of patients as the sample size, rather than the number of observations. The use of number of subjects in the calculation is a conservative approach, which provides a lower bound for the sample size. The ERG preferred method for deriving BIC is to use the number of observations in the calculation, although this approach provides an upper bound for the sample size.

The ERG notes that the model did not age-adjust utility values over time, however, this was not expected to have a large effect on the ICER due to the restricted time horizon of the model in the base case and the increased SMR used in the ERG's base case.

(2) Administration costs associated with the CBTA injections and uncertainty in the costs of administration of CBTA and of disease management

Within the model, administration costs for the CBTA injection were taken from NHS reference costs (2017-2018). These costs were assumed to consist of an outpatient consultation and an outpatient ultrasound scan. Whilst it is believed that the company intended to use the cost of a 'Consultant Led Non-Admitted Face-to-Face Attendance, Follow-up' (£148.01) to account for the outpatient consultation session cost, the company mistakenly inputted the cost of a 'Non-Face-to-Face' session (£102.96).

The revised model accounted for uncertainty in the costs of administering CBTA and the costs of disease management by using NHS Reference costs. However, the company have used the standard deviation, rather than the standard error in estimating the uncertainty around the mean, which is inappropriate for a cohort model. The ERG has estimated the standard error and has used these instead.

(3) The implementation of discontinuation of active treatment within the model due to poor response

In its model, the company applied discontinuation rates for CBTA + SoC, and glycopyrronium bromide + SoC, which were assumed to be independent of the severity state of sialorrhoea. Clinical advice provided to the ERG suggests that patients would be unlikely to continue with active treatment if they perceive it to be non-beneficial. Additionally, it would be unlikely that clinicians would persist with active treatment if the patient's condition remained severe.

In response to clarification question B2, the company amended this assumption. It applied a stopping rule for patients who are in the severe health state at a selected time point, but allowed patients with severe sialorrhoea before, and after, this time point to continue active treatment. The ERG believes it more appropriate that any stopping rule would also apply to subsequent time periods and has explored the impact of amending this assumption.

(4) The modelling approach for patients with mild sialorrhoea who discontinue active treatment

In response to the ERG's clarification questions, the company presented a revised version of the model, where it was assumed that patients who discontinue active treatment with mild / resolved sialorrhoea were modelled explicitly according to the transition probabilities for the SoC alone arm of the model, with an equal chance of transitioning from the mild / resolved to mild / resolved, moderate and severe

health states for the remainder of the time horizon. The ERG believes that assigning patients who discontinue active treatment with mild / resolved sialorrhoea to the moderate sialorrhoea state, and allowing transitions between the moderate and the severe states thereafter, would be more appropriate clinically and also removes the problem of having no data for patients with mild / resolved sialorrhoea.

(5) The implementation of the continuity correction in the transition probability matrices

In response to clarification question B3, the company added a continuity correction to rows (corresponding to 'from a given health state') of transition probability matrices where in any of the cells, one or more probabilities were zero. This was applied by adding a value of 1 to each cell in this row. The ERG prefers an approach of adding a new patient equally across all plausible health states to generate new transition probabilities to adjust for small numbers of transitions between states. The ERG introduced an additional change in assuming that it was not possible for patients receiving SoC only to ever be in a resolved / mild health state given that they had chronic, troublesome sialorrhoea. This may introduce a limitation related to stroke patients whose condition improves sufficiently that sialorrhoea is no longer a problem but clinical advice to the ERG suggested that the majority of patients with a stroke who improved would do so within the following six months.

(6) The patient population SMR value

Within its base case, the company applied an SMR value of 1. Whilst the ERG agrees that excess mortality is unlikely to be associated with sialorrhoea it is, however, likely to be associated with underlying conditions commonly present in patients with sialorrhoea.

(7) The proportion of patients requiring ultrasound scans when receiving CBTA

Within its base case, the company considered the cost of an ultrasound scan session for 56% of the cohort, equivalent to the actual figure from the SIAXI trial. However, the ERG received advice from its clinical experts that all patients might need ultrasound guidance to receive the CBTA injections.

(8) The variance of EQ-5D mean utility values

In its uncertainty estimation of the utility values derived from its LCMM model, the company arbitrarily assumed a 20% variance around the mean values. The ERG believes the approach is not appropriate, and that variance should be estimated directly from the LCMM model and comment that the company's approach resulted in a problem with the PSA caused by the inability of Excel to handle very small numbers.

(9) The acquisition costs of glycopyrronium bromide

The company assumed that the ratio of patients receiving glycopyrronium bromide as tablets or oral solution, was 1:1. The ERG believes that this assumption should be informed by national data sources such as Prescription Cost Analysis database.[29]

(10) Resource use associated with different severity levels of sialorrhoea

No resource use data were collected within SIAXI, however, the company assumed that improvements in sialorrhoea would reduce the number of speech pathology and occupational therapy consultations required. The company performed a sensitivity analysis assuming that the moderate and severe health states had the same resource requirements as feedback from clinical experts to the company suggested '*that there may not be a large difference in resource use between the management of severe and moderate sialorrhoea*'. However, the company always assumed a reduced number of consultations in the mild / resolved group. The ERG believes it plausible that these reductions may not happen if these consultations were combined with treatment for the underlying condition and have therefore explored the impact of this assumption on the ICER.

4.4 Exploratory analyses undertaken by the ERG

This section presents the methods and results of the ERG's exploratory analyses.

4.4.1 ERG's utility analysis

In order to inform the ERG's exploratory analyses, the ERG undertook additional analysis using the EQ-5D data collected in the SIAXI trial. The ERG fitted LCMMs to the individual patient-level data using the three sialorrhoea severity levels as explanatory variables rather than the raw DSFS sum scores so that the results do not rely on assuming each level of the DSFS sum scores would have equal number of patients. The health state grouping system was the same as in the CS (DSFS 2-3: mild/resolved; DSFS 4-6: moderate; DSFS 7-9: severe) All LCMMs were fitted using the 'lcmm' package in R. All LCMMs included covariates such as age, gender and aetiology as it was recommended to include all relevant covariates which were known to have an inference in the utility when performing the regression analysis.[30] BIC was calculated outside of the package as the 'lcmm' package provided the wrong calculation. The best fitting model was determined using Akaike Information Criterion (AIC) and BIC. The mean utility in each sialorrhoea severity state was calculated based on the best fitting LCMM. The standard error of the mean utility in each state was calculated using a Monte Carlo sampling approach given the estimated mean utility and variance covariance matrix from the fitted LCMM.

The ERG also re-calculated BIC for all of the company's models to select a best fitting model and estimated the mean utility for each sialorrhoea severity state using the company's approach.

The results of estimated mean utility are presented in Table 20. Goodness-of-fit assessment can be found in Appendix 1. The ERG's best fitting model for both health state grouping systems was the model with three latent classes with class-specific mean trends on severity, random effects on patient level and week, and fixed effects linear components including additional covariates such as age, gender and aetiology. After re-calculating the BIC for the company's models, the best fitting models was the three latent classes with random effects on patient-level and week (named model 1 in the CS). The ERG notes that using the company's BIC calculation, the BIC for model 1 and model 4 (the company's choice for best fitting model) had less than 1 point difference, which means that both models could be the best fitting models.

Table 20: Utility values based on ERG's exploratory analysis

		Grouping (DSFS 2-3: mild/resolved; DSFS 4-6: moderate; DSFS 7-9: severe)	
Model	Health state	Mean utility value	Difference compared with mild / resolved
ERG's	Mild/Resolved	0.6227	
	Moderate	0.5983	0.0244
	Severe	0.5774	0.0452
Company's model 1	Mild/Resolved	0.6218	
	Moderate	0.5882	0.0337
	Severe	0.5782	0.0436

4.4.2 Correcting administration costs of the CBTA injection and disease management costs

As indicated in Section 4.3.4, it is believed that the company used the wrong outpatient consultation cost within the model. The correct figure (£148.01) was used in the ERG's base case. The ERG also reduced the uncertainty in the costs related to administration of CBTA and of disease management costs by using the standard error rather than the standard deviation, as detailed in Section 4.3.4.

4.4.3 Assuming active treatment discontinuation for patients with severe sialorrhoea can happen after a selected time point

As indicated in Section 4.3.4, the company applied a stopping rule for patients with severe sialorrhoea on active treatment only at a certain time point. The ERG amended the model so that patients on active treatment would discontinue treatment if they have severe sialorrhoea four weeks after any injection after the first.

4.4.4 Amending the modelling assumption for patients with mild sialorrhoea who discontinue active treatment

As detailed in Section 4.3.4, the company's model assumed that patients with mild sialorrhoea who discontinued on active treatment continued treatment on SoC alone but remained in the mild health state for the rest of the model. The ERG amended the model, so that this cohort transitioned to the moderate health state once discontinuation happens.

4.4.5 Applying a modified continuity correction factor to the transition probability matrices

The ERG amended the model by adding a new patient equally across all plausible transitions from one health state to another to adjust for small numbers of transitions between states, resulting in an additional third of a patient being added to all transitions from CBTA + SoC. The ERG assumed that it was not possible for patients receiving SoC only to transition to a resolved / mild health state given that they had chronic, troublesome sialorrhoea, meaning that a half of a patient was added to the remaining transitions from the severe and moderate health states in the SoC transition matrix. The results from this amendment only have validity when the change detailed in Section 4.4.4 is made and thus the continuity correction analysis is run in conjunction with changing the assumption for people with mild sialorrhoea who discontinue active treatment

4.4.6 Adjusting the SMR input value to that of the decision problem intended population

For reasons indicated in Section 4.3.4, the ERG believes that the SMR value should be higher than 1. In response to clarification question A10, the company provided data from the literature regarding the SMR values for patients with Parkinson's disease or stroke. These figures were weighted by the ERG by the proportions of each condition within the SIAXI trial to estimate an SMR value of 4.09.

4.4.7 Assuming 100% of patients on CBTA require ultrasound guidance

As it is unclear whether the use of ultrasound may improve the efficacy of CBTA due to more accurate placement of the intervention this does not form part of the ERG's base case and is presented only as a scenario analysis.

4.4.8 Calculating the variance of EQ-5D mean utility values

As was indicated in Section 4.4.1, it was possible to calculate the standard errors of the mean utility values and these were used in the ERG's PSA without any calculation error.

4.4.9 Calculating the proportion of patients on different glycopyrronium formulations

For patients receiving glycopyrronium bromide, the ERG depended on the Prescription Cost Analysis of England in 2018 to estimate the ratio between patients receiving the tablet formulation and those on

the oral solution one.[29] From these data it was estimated that 38.32% of the patients receive the tablet formulation and 61.68% receive the liquid formulation.

4.4.10 Assuming the same resource use regardless of sialorrhoea severity

In a scenario analysis, the ERG explored the impact of using the same resource use for mild, moderate, and severe sialorrhoea. This scenario assumed no additional consultations specifically for sialorrhoea per model cycle but was not included in the ERG's base case.

5 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

All results were run deterministically with the ERG also running probabilistic analyses for its entire base case. The probabilistic values were similar to the deterministic ones implying linearity within the model. A summary of the exploratory analyses undertaken by the ERG is presented for in Table 21 for severe patients and in Table 22 for moderate patients. In all scenarios, CBTA + SoC was dominant compared to glycopyrronium + SoC. Therefore, for simplicity, the ICER presented in both tables is comparing CBTA + SoC versus SoC alone.

5.1 Interpreting the results for the deterministic analyses

It is seen that the key driver of the ICER for CBTA + SoC compared with SoC alone is the assumed utility values associated with the severity of sialorrhoea. The company put forward reasons as to why the EQ-5D-3L may be insensitive to changes in the severity of sialorrhoea, however, the ERG cannot rule out the possibility that the change in utility between severe and mild/resolved is small and is accurately captured.

For patients with severe sialorrhoea the deterministic ICER of CBTA compared with SoC was over £44,000 using the utility values generated directly from the SIAXI RCT and below £9,000 when using the NG62 derived data; these values were above £50,000 and below £11,000 for patients with moderate sialorrhoea. In the combined severity patient population, the ICER value was over £47,000 using the utility values from the ERG's LCMM model, and below £10,000 using the utility values from the NG62 model. The ICERs would increase if all CBTA injections were guided with ultrasound and there was no increase in effectiveness of CBTA and also if resource use did not alter based on sialorrhoea severity.

CBTA dominated glycopyrronium bromide regardless of the utility values assumed.

5.2 ERG base case probabilistic results

The ERG carried out 1,000 PSA iterations using its base case assumptions. Cost-effectiveness acceptability curves and CE planes are presented in Appendix 2. For patients with severe sialorrhoea the probabilistic ICER of CBTA compared with SoC was over £41,000 using the utility values generated directly from the SIAXI RCT; this value was above £48,000 for patients with moderate sialorrhoea. In the combined severity patient population, the ICER value was over £45,000. CBTA dominated glycopyrronium bromide regardless of the utility values assumed. The ICERs would increase if all CBTA injections were guided with ultrasound and there was no increase in effectiveness of CBTA and also if resource use did not alter based on sialorrhoea severity.

Based on the probabilistic version of the model, compared with SoC alone, the probability of CBTA + SoC to be cost-effective at a cost per QALY gained threshold of £20,000 was 0.02 and 0.01 for severe and moderate patients respectively. At a threshold pf £30,000, the respective probabilities were 0.15 and 0.12.

Compared with glycopyrronium bromide + SoC, CBTA + SoC was found to be cost-effective in 100% of the PSA iterations for both severe and moderate patients using a cost per QALY gained threshold of £20,000.

Table 21: Exploratory model results for severe patients

Analysis	Discounted costs			Discounted QALYS			ICER (CBTA + SoC versus SoC)
	CBTA + SoC	Glyc Br + SoC	SoC	CBTA + SoC	Glyc Br + SoC	SoC	
Company base case	£6,135	£15,020	£3,070	3.510	3.318	3.175	**£9,162**
1) Using the company's LCMM model	£6,135	£15,020	£3,070	4.967	4.914	4.876	£33,646
2) Applying the ERG's LCMM utility values	£6,135	£15,020	£3,070	4.914	4.875	4.846	£45,275
3) Correcting CBTA administration costs	£6,804	£15,020	£3,070	3.510	3.318	3.175	£11,160
4) Severe patients discontinue active treatment after second treatment cycle	£5,095	£10,693	£3,070	3.405	3.268	3.175	£8,828
5) Mild patients who discontinue active treatment, transition to the moderate health state[]	£6,130	£15,013	£3,070	3.515	3.323	3.175	£9,018
6) Applying the modified correction factor*	£6,150	£15,108	£3,210	3.507	3.287	3.125	£7,681
7) Adjusting the population's SMR value	£5,254	£13,146	£2,544	2.898	2.732	2.610	£9,390
8) Correcting the acquisition costs for glycopyrronium bromide	£6,135	£14,076	£3,070	3.510	3.318	3.175	£9,162
ERG base case (scenarios 2 – 8)	£5,013	£9,505	£2,661	4.035	4.003	3.982	**£44,492**
ERG base case (probabilistic results)	£4,823	£9,331	£2,466	3.738	3.703	3.681	**£41,335**
ERG base case (using the NG utility values, i.e. excluding scenarios 1 and 2)	£5,013	£9,505	£2,661	2.830	2.673	2.567	**£8,963**
9) Assuming all patients require an ultrasound scan for the CBTA injections†	£5,243	£9,505	£2,661	4.035	4.003	3.982	£48,845
10) Assuming no additional resource use for the different sialorrhoea severity levels†	£3,012	£7,110	£0	4.035	4.003	3.982	£56,960

[] This produces more QALYs than the base case due to the continuity correction applied in the mild health state * In conjunction with scenario 5 †In conjunction with the ERG base case
CBTA, Clostridium botulinum toxin A; Glyc Br, Glycopyrronium Bromide; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, Standard of Care

Table 22: Exploratory model results for moderate patients

Analysis	Discounted costs			Discounted QALYS			ICER (CBTA + SoC versus SoC)
	CBTA + SoC	Glyc Br + SoC	SoC	CBTA + SoC	Glyc Br + SoC	SoC	
Company base case	£6,064	£14,900	£2,939	3.542	3.371	3.233	**£10,130**
1) Using the company's LCMM model	£6,064	£14,900	£2,939	4.970	4.920	4.882	£35,425
2) Applying the ERG's LCMM utility values	£6,064	£14,900	£2,939	4.919	4.884	4.856	£49,329
3) Correcting CBTA administration costs	£6,732	£14,900	£2,939	3.542	3.371	3.233	£12,296
4) Severe patients discontinue active treatment after second treatment cycle	£5,090	£11,306	£2,939	3.444	3.330	3.233	£10,216
5) Mild patients who discontinue active treatment, transition to the moderate health state[]	£6,058	£14,893	£2,939	3.546	3.376	3.233	£9,959
6) Applying the modified correction factor*	£6,075	£14,974	£3,061	3.540	3.346	3.190	£8,609
7) Adjusting the population's SMR value	£5,183	£13,028	£2,414	2.930	2.784	2.667	£10,525
8) Correcting the acquisition costs for glycopyrronium bromide	£6,064	£13,956	£2,939	3.542	3.371	3.233	£10,130
ERG base case (scenarios 2 – 8)	£5,013	£10,001	£2,515	4.041	4.014	3.992	**£50,955**
ERG base case (probabilistic results)	£4,854	£9,563	£2,313	3.744	3.714	3.691	**£48,127**
ERG base case (using the NG utility values, i.e. excluding scenarios 1 and 2)	£5,013	£10,001	£2,515	2.869	2.740	2.632	**£10,534**
9) Assuming all patients require an ultrasound scan for the CBTA injections†	£5,250	£10,001	£2,515	4.041	4.014	3.992	£55,791
10) Assuming no additional resource use for the different sialorrhoea severity levels†	£3,103	£7,759	£0	4.041	4.014	3.992	£63,278

[] This produces more QALYs than the base case due to the continuity correction applied in the mild health state *In conjunction with scenario 5 †In conjunction with the ERG base case
CBTA, Clostridium botulinum toxin A; Glyc Br, Glycopyrronium Bromide; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, Standard of Care

5.3 One-way deterministic sensitivity analysis

The ERG's tornado diagrams are presented in Appendix 3 (assuming a cost per QALY gained threshold of £20,000) and Appendix 4 (assuming a cost per QALY gained threshold of £30,000). Within the tornado diagrams, the ERG used the same uncertainty measures assumed in the CS for all parameters except utility values. The utility variances from the ERG's LCMM analysis were used to construct the 95% CI whose bounds were used in the sensitivity analysis.

The findings from this sensitivity analysis shows that the deterministic base case results appear robust. The NMB associated with CBTA + SoC arm was higher than glycopyrronium bromide + SoC arm for all scenarios. Compared with SoC alone, the tornado plots show that CBTA + SoC is not cost-effective in all scenarios.

5.4 Threshold analysis

To acknowledge that it may be plausible that the EQ-5D-3L is insensitive to chronic sialorrhoea improvement a threshold analysis was undertaken which increased the utility difference between the resolved/mild health state and the moderate health state. In this analysis the utility differences (based on the ERG's LCMM analysis) were increased between the moderate health state and the severe health state by a common factor – thus maintaining the ratio between moderate and severe sialorrhoea. This factor was increased until the ICER of CBTA + SoC compared with SoC was equal to £20,000 and £30,000 per QALY gained with the analyses undertaken for a moderate group of patients and for a severe group of patients. At an ICER of £20,000 per QALY, the multiplication factor required was 2.22 for patients with severe sialorrhoea, 2.55 for patients with moderate sialorrhoea and 2.37 for all patients with moderate or severe sialorrhoea. These factors were 1.48, 1.7 and 1.58 at an ICER of £30,000 for patients with severe, moderate, and moderate/severe sialorrhoea respectively. The disutilities that these multipliers equate to are provided in Table 23 and Table 24.

Table 23: The disutilities required with the sialorrhoea severity states in order to reach a cost per QALY gained value of £20,000

	An initial population with severe sialorrhoea	An initial population with moderate sialorrhoea	An initial population with severe or moderate sialorrhoea
Disutility associated with moderate sialorrhoea†	0.046	0.053	0.049
Disutility associated with severe sialorrhoea†	0.101	0.115	0.107

† Compared with mild / resolved sialorrhoea.

Table 24: The disutilities required with the sialorrhoea severity states in order to reach a cost per QALY gained value of £30,000

	An initial population with severe sialorrhoea	An initial population with moderate sialorrhoea	An initial population with severe or moderate sialorrhoea
Disutility associated with moderate sialorrhoea†	0.036	0.041	0.039
Disutility associated with severe sialorrhoea†	0.067	0.077	0.071

† Compared with mild / resolved sialorrhoea.

6 END OF LIFE

The company made no claims that CBTA would meet the end of life criteria as it was assumed that the intervention would not extend life. The ERG concurs with the company's view.

7 OVERALL CONCLUSIONS

The clinical evidence for CBTA was based on one placebo-controlled RCT, SIAXI, which was of good methodological quality, and whose population was considered generalisable to a UK population of Parkinson's disease and stroke patients, with chronic sialorrhoea. The ERG notes that more aetiologies of sialorrhoea would be eligible for treatment with the licence for CBTA. The effectiveness of comparator interventions was studied in only a few poor quality RCTs of short duration that did not allow an indirect comparison with CBTA.

SIAXI showed a statistically significant advantage for CBTA 100U over PBO for uSFR and participant's GICS score. The most commonly reported adverse events (AEs) in the CBTA 100U group were tooth extraction, dry mouth, diarrhoea and hypertension. During the 16-week placebo-controlled phase of the RCT, none of the SAEs were considered treatment-related.

[redacted] The company stated that the EQ-5D-3L would be insensitive to improvements in the severity of sialorrhoea but the ERG notes that the 1.04 change for CBTA in the patients GICS is marginally above minimally improved function (i.e. a change of 1), whilst the change for PBO patients was 0.47. Using the alternative approach based on NG62 data also indicated that the elimination of severe sialorrhoea would have a similar impact on utility as if the patient had never experienced a stroke or did not have Parkinson's disease, which may not be plausible.

The use of the EQ-5D-3L data from SIAXI increased the ICER of CBTA + SoC compared with SoC alone in the company model to over £33,000 (a cost increase (ΔC) of £3,066 and a QALY gain (ΔQ) of 0.091 in patients with severe sialorrhoea and to over £35,000 (ΔC £3,125; ΔQ 0.088) in patients with moderate sialorrhoea. Using the ERG-preferred base case the probabilistic ICER increased to over £41,000 (ΔC £2,357; ΔQ 0.057) for patients with severe sialorrhoea and to over £48,000 (ΔC £2,541; ΔQ 0.053) for people with moderate sialorrhoea.

Threshold analyses on the ERG's deterministic base case indicates that the increase in disutility compared to the resolved / mild severity state to the remaining health states would need to be increased by a factor of 2.22 for patients with severe sialorrhoea to achieve a cost per QALY gained of £20,000 for CBTA + SoC vs SoC alone. For patients with moderate sialorrhoea this value was 2.55, and it was 2.37 for patients with severe or moderate sialorrhoea. These factors reduced to 1.48, 1.7 and 1.58 respectively assuming a threshold of £30,000 per QALY gained.

The ERG's analyses indicated that CBTA was likely to dominate glycopyrronium bromide + SoC in that, on average, CBTA + SoC produced an increase in health and saved money The results of the

probabilistic analyses were: for patients with severe sialorrhoea (ΔC -£4,508; ΔQ 0.035) and for patients with moderate sialorrhoea (ΔC -£4,709; ΔQ 0.03). Therefore, if a clinician was considering the use of glycopyrronium bromide + SoC it appears that using CBTA + SoC would be a better option.

Further considerations associated with the use of CBTA + SoC may be to ensure that patients who have sustained a stroke have had a sufficient duration of time since the incidence to be confident that the sialorrhoea would not resolve itself as a patient's condition improved. It may be prudent to monitor the number of tooth extractions that are required by patients receiving CBTA + SoC to be confident that these are not associated with the treatment.

7.1 Implications for research

The key uncertainty within the analyses relates to the decrement in utility associated with chronic sialorrhoea, which the company do not believe are adequately captured within the EQ-5D-3L. The ERG does not believe that this has been conclusively proven. Using a more sensitive measure, such as the EQ-5D-5L in future research, may help to resolve some of this uncertainty.

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9 APPENDICES

Appendix 1: ERG's exploratory analysis on estimating mean utility

The LCMMs used in the ERG's exploratory analysis are presented in Table 25. The best fitting model was chosen based on AIC and BIC. In both health state grouping systems, the model with 2 latent classes had the lowest BIC and the model with 3 latent classes had the lowest AIC. The model with 3 latent classes predicted mean utility slightly better than the model with 2 latent classes according to the p-value of the explanatory variable (severity). Hence, the model with 3 latent classes was chosen as the best fitting model.

Table 25: ERG's LCMMs to predict mean utility from sialorrhoea severity health states

Model	Linear component	Number of latent classes	Class membership	Class-specific linear component	Random effects	AIC	BIC
1	~ severity + age + gender + aetiology	1	NA	NA	~1|id	-672.725	-625.624
2	~ severity + age + gender + aetiology	1	NA	NA	~1+week|id	-691.631	-634.062
3	~ severity + age + gender + aetiology	2	NA	~severity	~1+week|id	-724.14	**-645.633**
4	~ severity + age + gender + aetiology	3	NA	~severity	~1+week|id	**-740.96**	-641.526
5	~ severity + age + gender + aetiology	3	~ age + gender + aetiology	~severity	~1+week|id	-727.21	-585.907

Abbreviations: NA: not applicable; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; DSFS: Drooling Severity and Frequency Scale.
Note: Bold indicates the best fitting model.
Severity Grouping (DSFS 2-3: mild/resolved; DSFS 4-6: moderate; DSFS 7-9: severe)

The re-calculated BIC values for the company's LCMMs are presented in Table 26.

Table 26: Goodness-of-fit results for the company's LCMMs

Model	Maximum log-likelihood	AIC	BIC
1	368.78	**-705.57**	**-621.831**
2	354.18	-680.36	-607.091
3	354.18	-684.36	**-621.558**
4	405.66	-751.32	-594.316
5	398.99	-741.97	-595.434
6	370.84	-705.69	-612.609
7	371.41	-702.81	-597.02
8	369.01	-702.03	-607.824

Abbreviations: NA: not applicable; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion.
Note: Bold indicates the best fitting model.

Appendix 2: ERG's probabilistic results

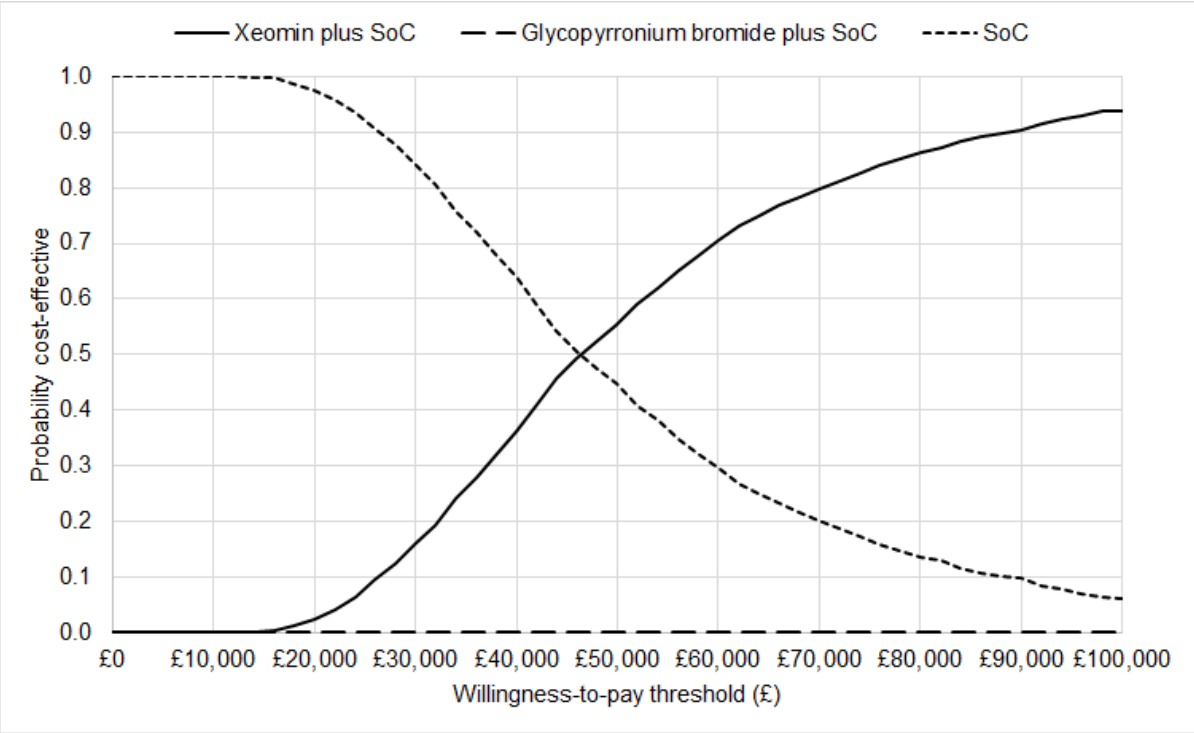

Figure 8: ERG's base case cost–effectiveness acceptability curve (severe patients)

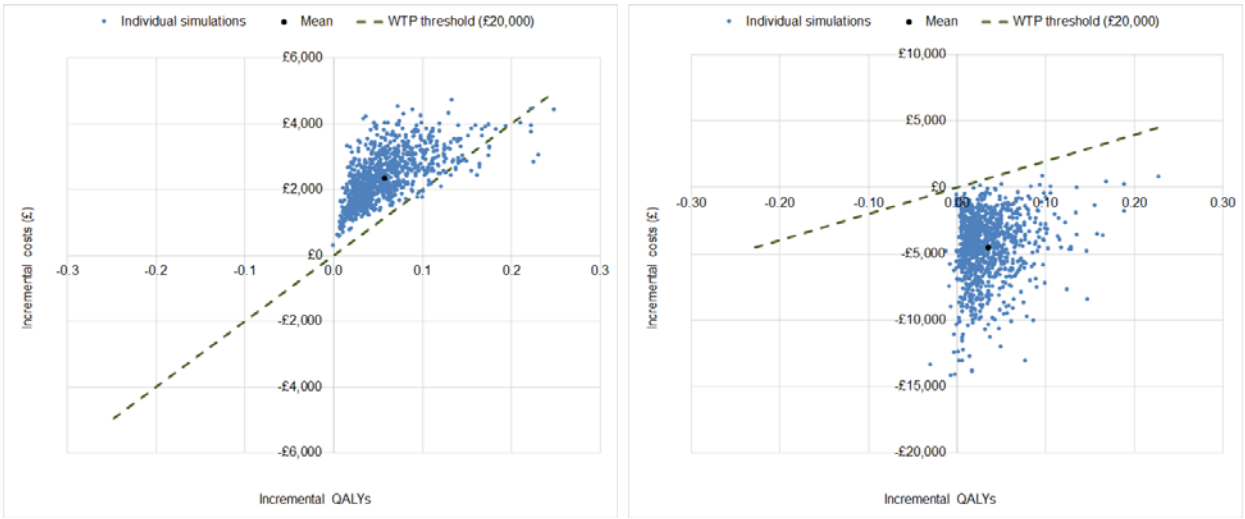

Figure 9: ERG's cost-effectiveness planes of CBTA + SoC (severe patients) versus (i) SoC alone (left side) (ii) glycopyrronium bromide (right side)

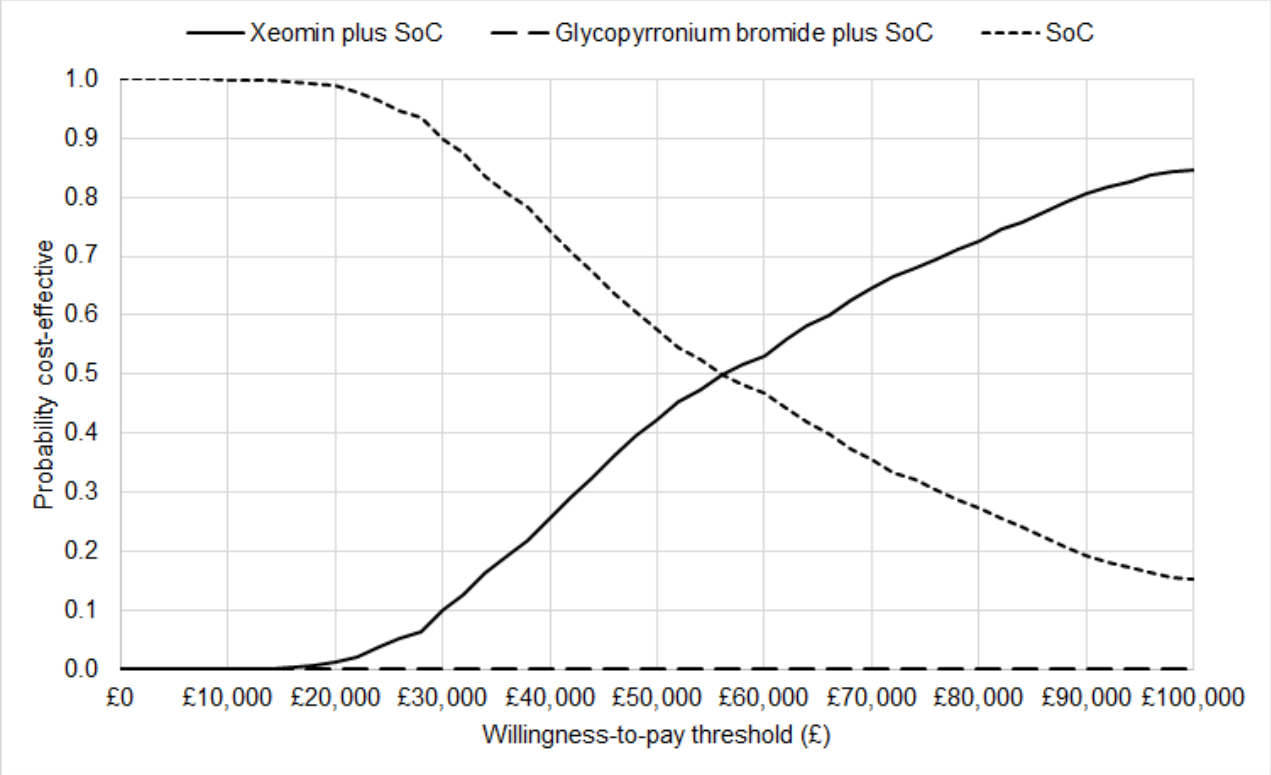

Figure 10: ERG's base case cost–effectiveness acceptability curve (moderate patients)

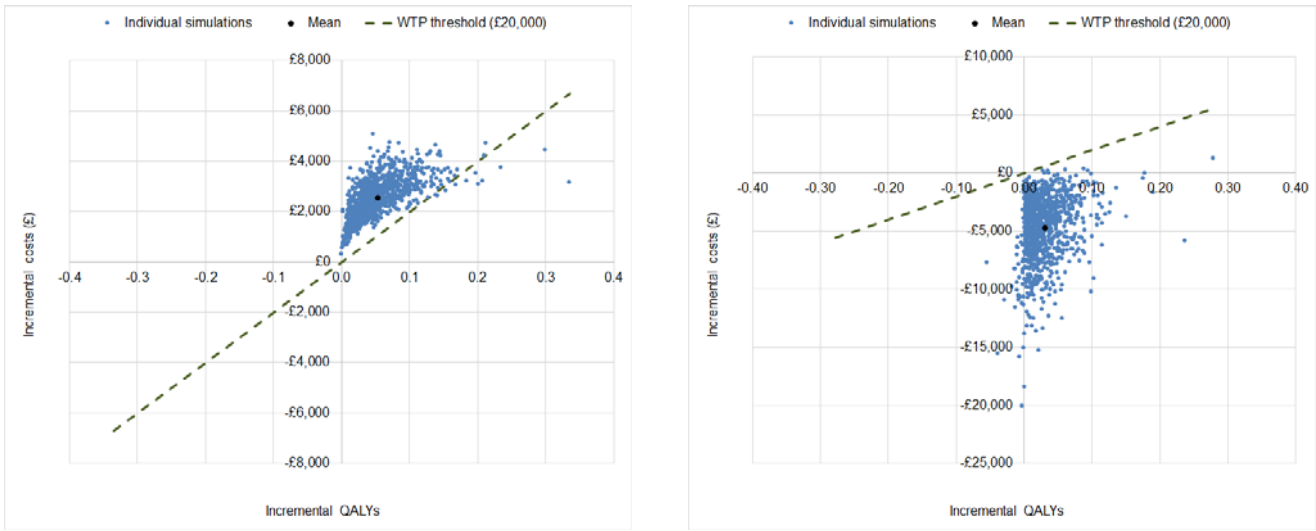

Figure 11: ERG's cost-effectiveness planes of CBTA + SoC (moderate patients) versus (i) SoC alone (left side) (ii) glycopyrronium bromide (right side)

Appendix 3: ERG's one-way sensitivity analyses (tornado plots) at the £20,000/QALY threshold

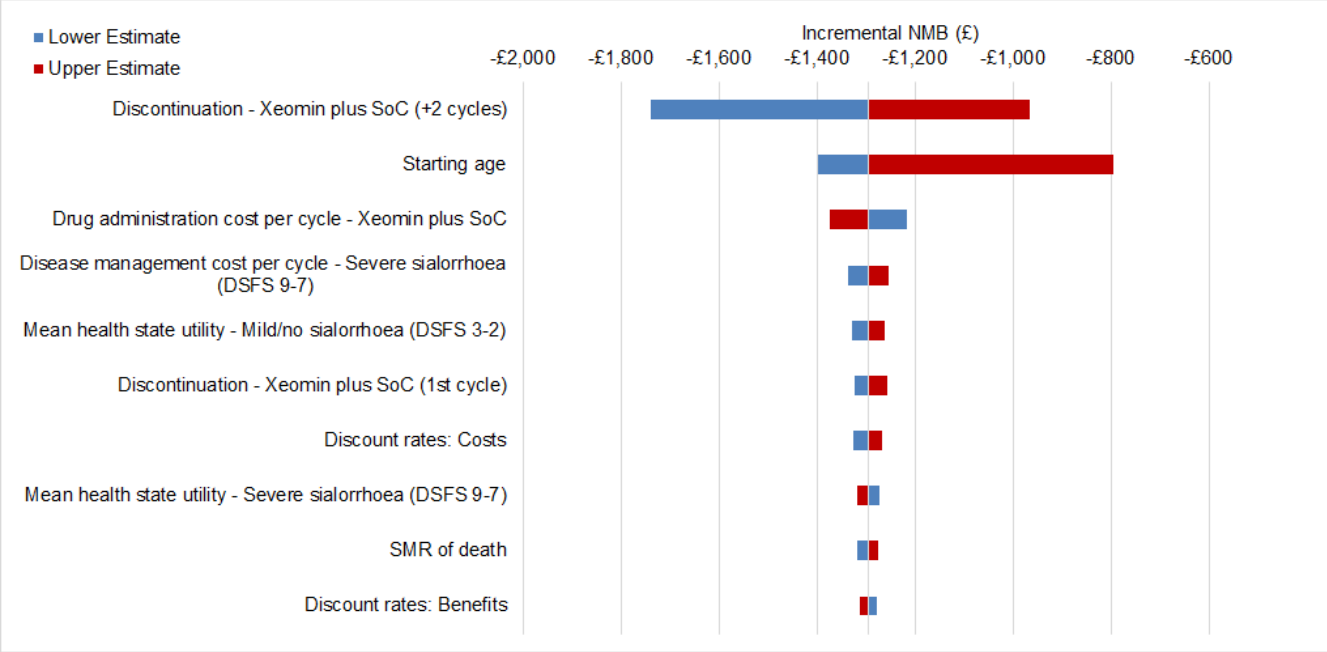

Figure 12: CBTA plus SoC vs. SoC tornado plot (ERG base case - severe patients)

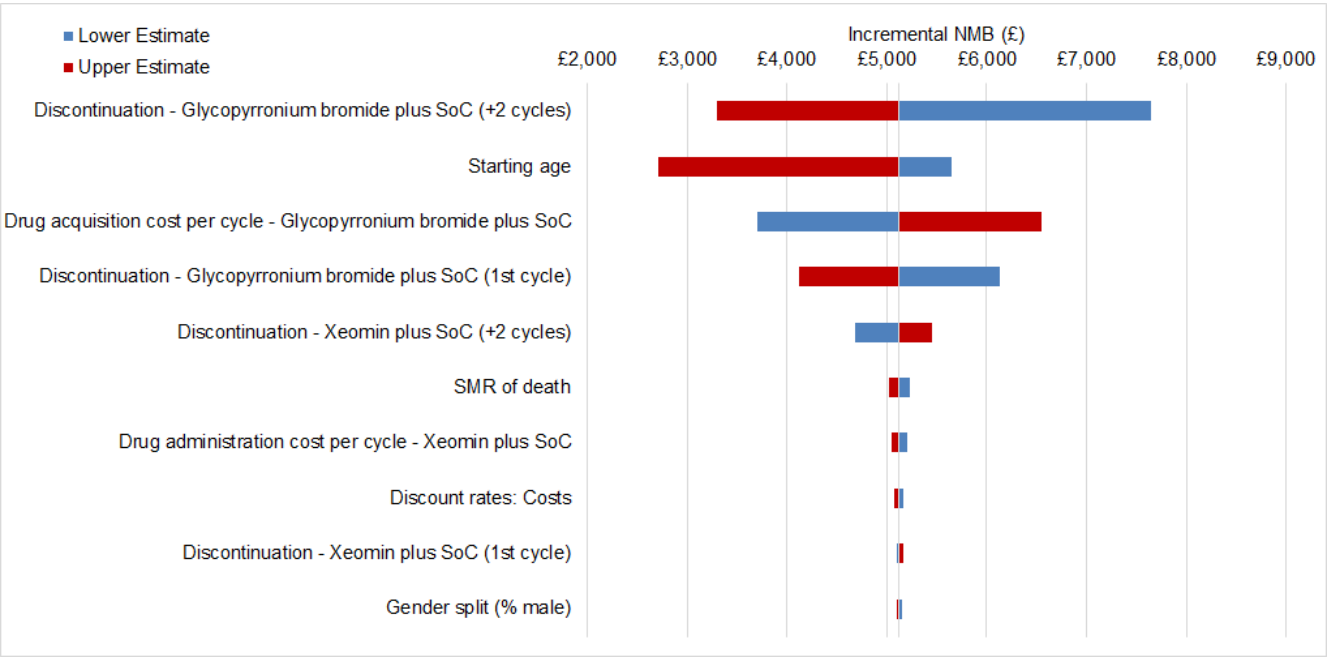

Figure 13: CBTA plus SoC vs. glycopyrronium bromide tornado plot (ERG base case - severe patients)

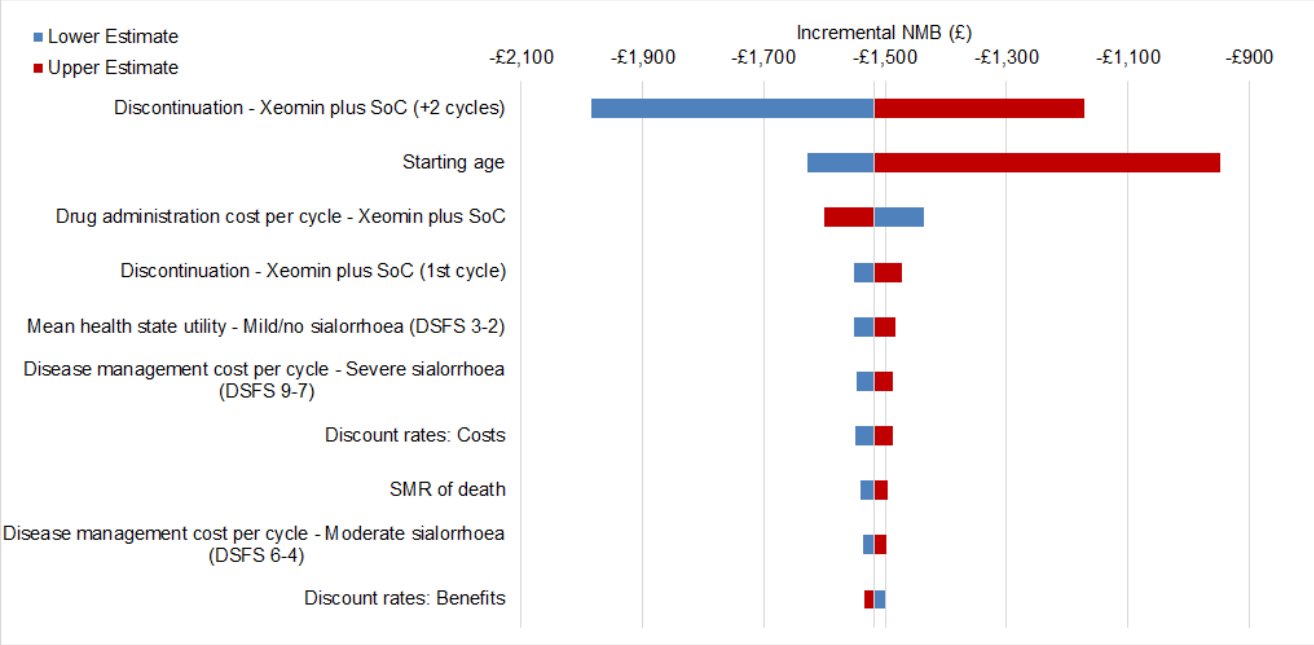

Figure 14: CBTA plus SoC vs. SoC tornado plot (ERG base case - moderate patients)

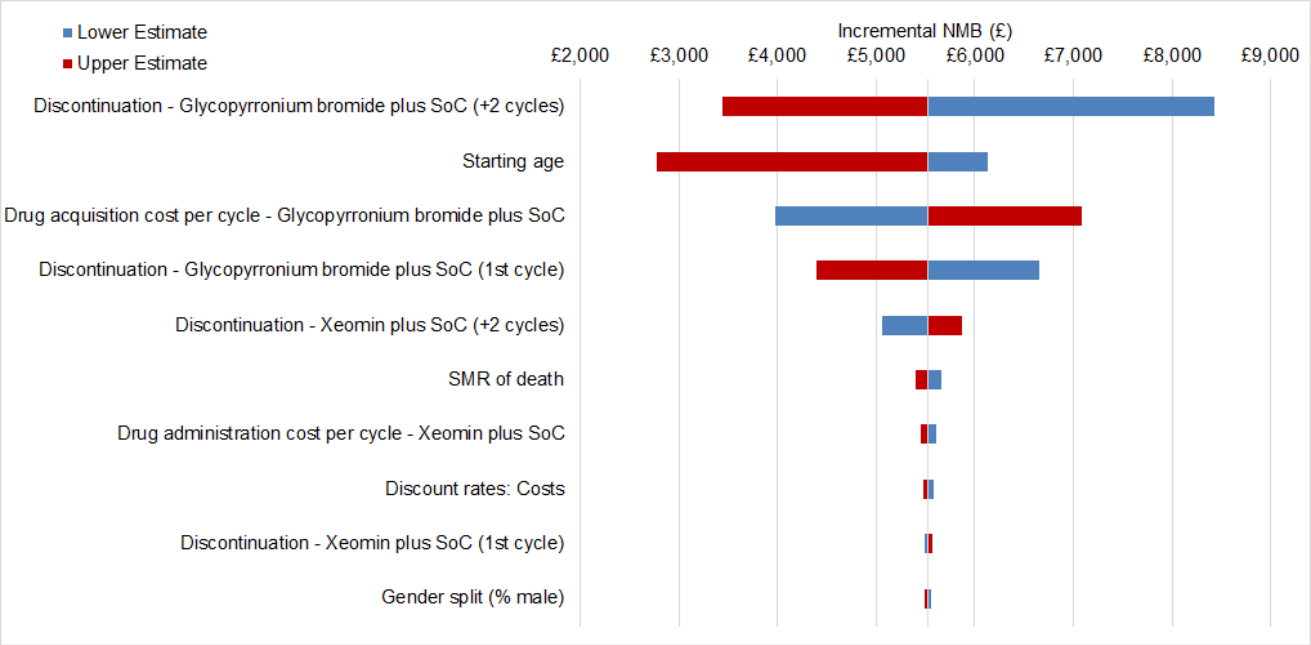

Figure 15: CBTA plus SoC vs. glycopyrronium bromide tornado plot (ERG base case - moderate patients)

Appendix 4: ERG's one-way sensitivity analyses (tornado plots) at the £30,000/QALY threshold

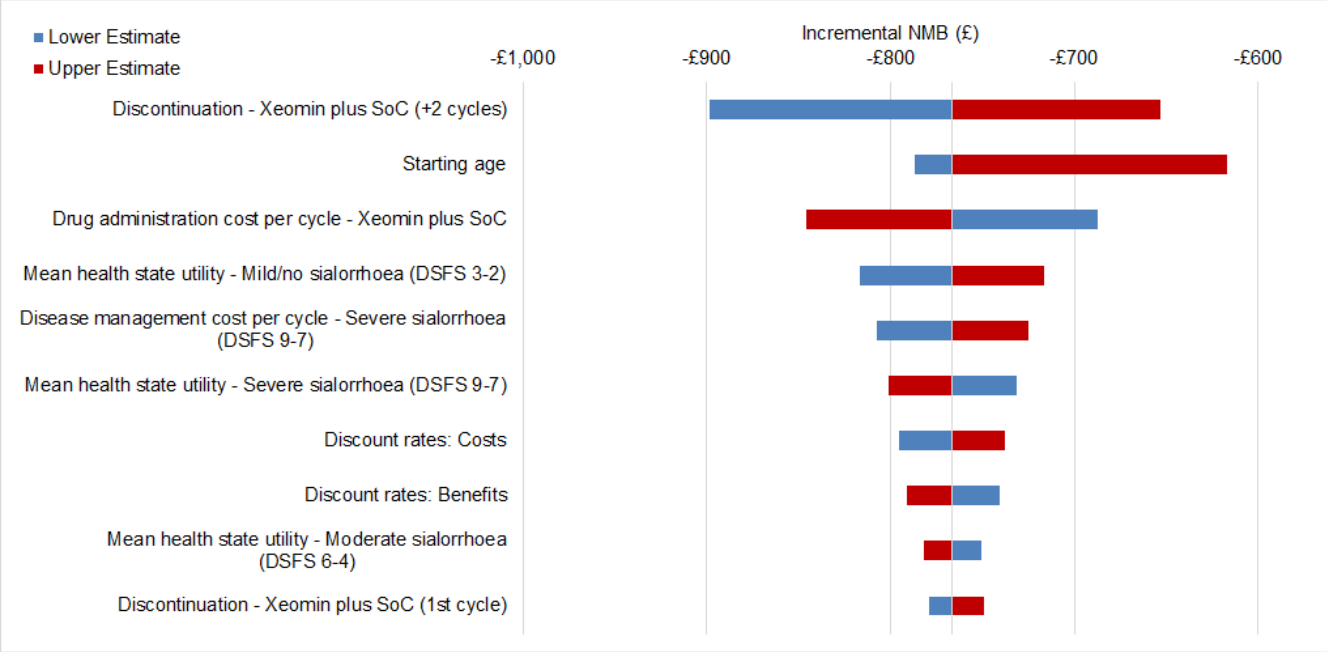

Figure 16: CBTA plus SoC vs. SoC tornado plot (ERG base case - severe patients)

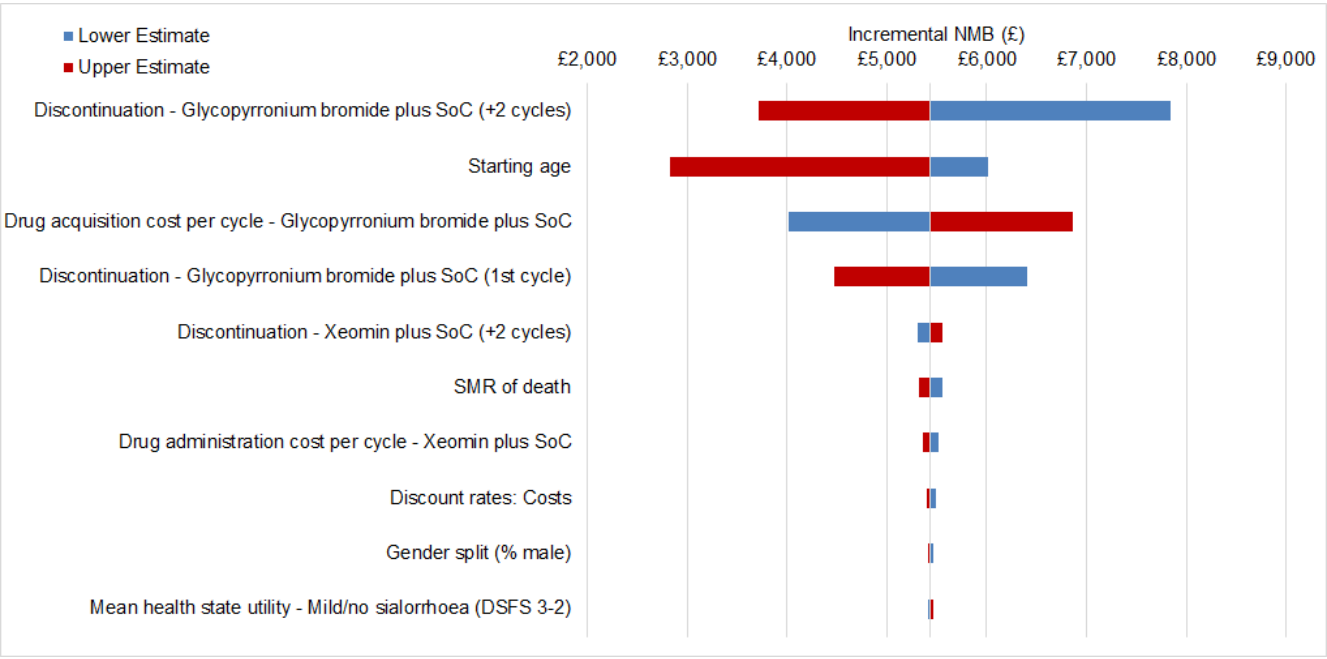

Figure 17: CBTA plus SoC vs. glycopyrronium bromide tornado plot (ERG base case - severe patients)

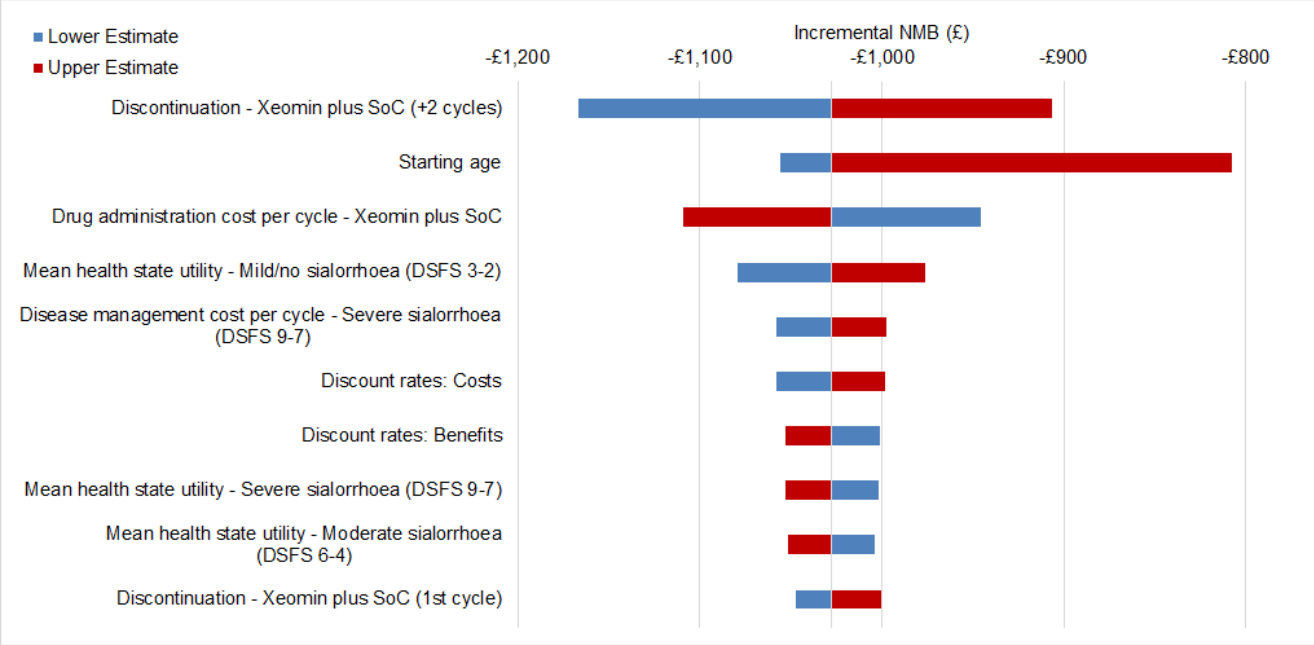

Figure 18: CBTA plus SoC vs. SoC tornado plot (ERG base case - moderate patients)

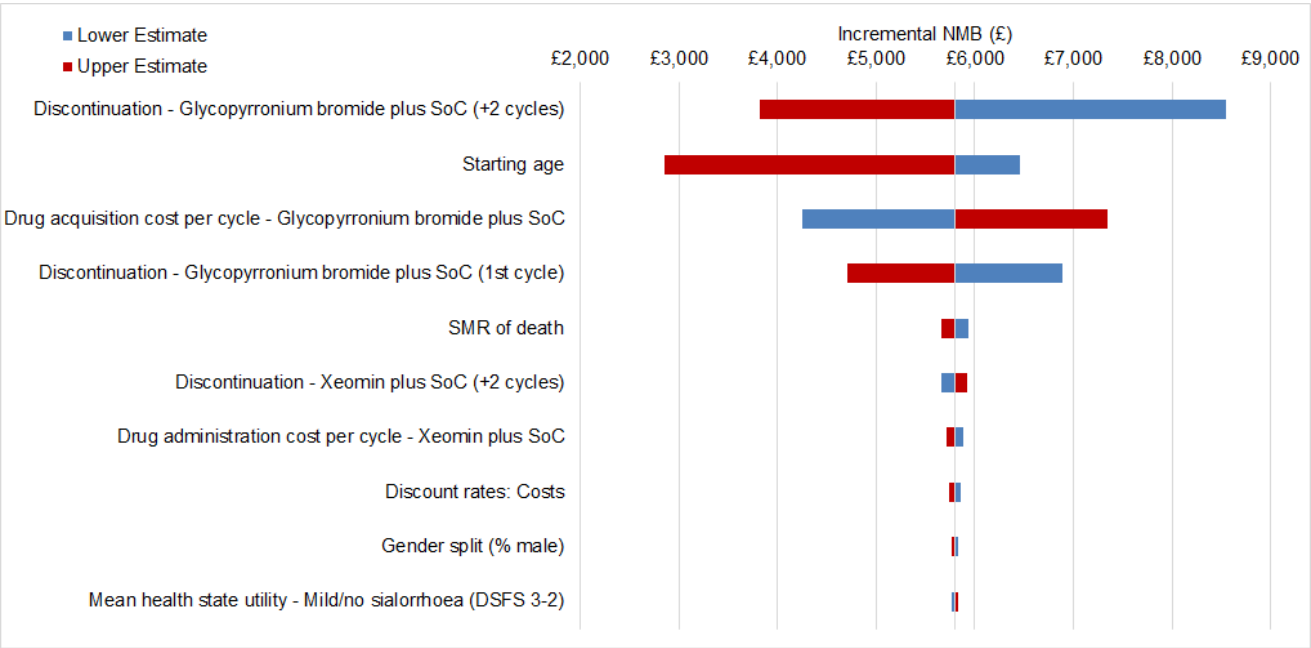

Figure 19: CBTA plus SoC vs. glycopyrronium bromide tornado plot (ERG base case - moderate patients)

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Clostridium botulinum neurotoxin type A for treating chronic sialorrhoea [ID1150]

You are asked to check the ERG report from School of Health and Related Research (ScHARR) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 1 May 2019** using the below proforma 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.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Section 1: Major comments

Issue 1 Description of the modelling approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 41. *"patients who discontinued active treatment were modelled using three severity-based health states with the proportions estimated as the steady state in a closed population calculated from the transition probabilities for the SoC alone arm"* Page 42. *"The submitted model adopts a cohort-level Markov state transition approach which consists of five health states: (1) mild/resolved sialorrhoea; (2) moderate sialorrhoea; (3) severe sialorrhoea; (4) Treatment discontinuation; and (5) dead."* Page 43. *"Patients could transition from any of the three severity-related health state to a fourth state representing treatment discontinuation, which also tracked the patients sialorrhoea severity, using the same three*	This statement is factually inaccurate, and should be amended as follows: *"patients who discontinued active treatment were explicitly modelled across the three severity-based health states according to the transition probabilities for the SoC alone arm of the model"* Page 42. Similarly, this statement should be amended as follows: *"The submitted model adopts a cohort-level Markov state transition approach which consists of seven health states: (1) mild/resolved sialorrhoea; (2) moderate sialorrhoea; (3) severe sialorrhoea; (4)–(6) Treatment discontinuation (mild/resolved, moderate and severe sialorrhoea); and (7) dead."* Page 43. It would be more accurate to describe the model with three separate health states (for each sialorrhoea severity) to model treatment discontinuation.	In response to the ERG's clarification questions, the model was updated such that patients in the active treatment arms who discontinue no longer transitioned to a dedicated 'Discontinued' health state, and instead were explicitly modelled across the three severity-based health states according to the transition probabilities for the SoC alone arm of the model. We understand that the model structure diagram presented in the ERG report is from the original submission and has not been updated since the clarification questions.	Apologies for the inaccurate description of the revised model. The text has been changed as suggested

groupings as before discontinuation." Page 43. The model structure diagram is now inaccurate.	Page 43. Please amend the model structure diagram to show three separate health states (for each sialorrhoea severity) for treatment discontinuation, or add a footnote such as: *"Footnote: patients who discontinued active treatment continued to be explicitly modelled across the three severity-based health states"*		

Issue 2 Description of the modelling approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 44. *"Glycopyrronium bromide used the same transition matrices of CBTA but with the probabilities of health state improvements to be 75% of the CBTA values with the remaining 25% staying in the same health state"*	This statement is factually inaccurate, and should be amended as follows: *"glycopyrronium bromide used the same transition matrices of CBTA but with the probabilities of health state improvements to be 75% of the CBTA values with the remaining 25% either staying in the same health or improving by only one health state for prior 1-state and 2-state improvements, respectively"*	For the 25% who experience lower efficacy in the glycopyrronium bromide plus SoC arm of the model, they either remain in the same health state if the transition was a 1-state improvement (moderate to mild/resolved or severe to moderate), or improve 1 health state only if the transition was a 2-state improvement (severe to mild/resolved).	Similar text to that proposed has been added.

Issue 3 Omission of relevant context relating to GICS data from the SIAXI trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 58. *"Whilst the GICS score at Week 4 results within the SIAXI trial showed a statistically significant improvement in the CBTA 100U group compared with*	This discussion should be amended to also note that consistent positive GICS scores (which measure the impression of change compared to the status before the previous injection and are therefore cumulative) were	The ERG have reported and contextualised GICS data from only one timepoint in the SIAXI trial (Week 4) in their discussion on coherence of GICS and EQ-5D	Additional AIC data have been discussed relating to the EP to provide further context.

the placebo group, this may not be clinically important. The absolute score for the CBTA 100U group was [redacted] and the difference in score compared with PBO was [redacted], which may not be large enough to have a meaningful change in function. The ERG believes that the observed EQ-5D-3L data in SIAXI (i.e. small gain in mean utility across sialorrhoea severity health states) are coherent with the observed patient's GICS scores"	observed across the EP. [redacted]	scores. As such, they have omitted relevant data that is also important to the discussion. The ERG state that the GICS scores at Week 4 "*may not be large enough to represent a meaningful change in function"*, but do not note the consistent, and importantly, cumulative, positive GICS scores observed in the EP and that this pattern was not observed with EQ-5D. These GICS scores, the improvements in other trial outcomes (including uSFR and DSFS) and the high trial retention rate ([redacted]% overall), indicate a clinically meaningful improvement in sialorrhoea as a result of treatment with Xeomin, and thus Merz believe the observed EQ-5D-3L data do not match clinical expectations. Whilst Merz acknowledge there is a lack of empirical evidence, a clear rationale exists for the insensitivity of the generic EQ-5D instrument to changes in sialorrhoea severity, and insensitivity has been demonstrated in disorders that, like sialorrhoea, are neither painful nor life-threatening. By not presenting all relevant data, the ERG's statement represents an incomplete and hence inaccurate	We do not believe the remaining amendments are a factual inaccuracy and note the wide standard errors around the EQ VAS data presented in Table 25 of the company submission. We have discussed the potential insensitivity of the EQ-5D for patients with sialorrhoea in our report, and this should now be a judgement for the committee.

		summary of the considerations relating to GICS and EQ-5D.	

Issue 4 Description of the LCMM analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 59. *"the 'lcmm' package in R calculated BIC wrongly. Instead of using the number of observations in the calculation, the number of patients was used. Selecting the best fitting model based on the BIC calculated within the 'lcmm' package could therefore be misleading."*	Merz believe that this statement is inaccurate and should be amended as follows: *"the 'lcmm' package in R calculated BIC using the number of patients, rather than number of observations in the calculation. Given that the lcmm models do not assume independence of observations, the use of the number of patients to derive BIC in a longitudinal framework may be appropriate from a theoretical standpoint. However, the ERG's preferred method for deriving BIC is to use the number of observations in the calculation."*	No justification has been provided as to why the use of the number of patients in the calculation of BIC would be considered wrong. It is our understanding that this approach is not incorrect, but either approach may be valid. This should be reflected in the wording of the ERG report. Using the number of patients to derive the BIC for longitudinal models is a standard approach in the field. For example, as well as being the default for the 'lcmm' package, it is also the default method in the SAS procedure PROC MIXED when there are repeated observations.[1] Using the number of patients rather than the total number of observations is also justifiable from the standpoint of requiring independence only between patients (not between observations) in the derivation of the BIC for longitudinal data.[2] However, Merz acknowledge that the use of the number of	The text has been amended to reflect that there are multiple ways to calculate BIC for longitudinal data.

		observations may also be appropriate.[3]	

Issue 5 Description of the modelling approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 60. *"The company presented a revised version of the model, where it was assumed that patients who discontinue active treatment with mild / resolved sialorrhoea will maintain mild / resolved sialorrhoea for the remaining time horizon, despite only receiving SoC"* Page 63. *"4.4.4 Correcting the modelling assumption for patients with mild sialorrhoea who discontinue active treatment* *As detailed in Section 4.3.4, the company's model assumed that patients with mild sialorrhoea who discontinued on active treatment continued treatment on SoC alone but remained in the mild health state for the rest of the model."*	These statements are factually inaccurate, and thus should be removed from the ERG report, or amended as follows (on page 60 and 63): *"the company presented a revised version of the model, where it was assumed that patients who discontinue active treatment with mild / resolved sialorrhoea were modelled explicitly according to the transition probabilities for the SoC alone arm of the model, with an equal chance of transitioning from the mild / resolved to mild / resolved, moderate and severe health states for the remainder of the time horizon"* There are no data available to inform these transition probabilities, and thus the chosen values are based on assumptions. As such, if the ERG still believes that assigning patients who discontinue active treatment with mild / resolved sialorrhoea to the moderate sialorrhoea state, and allowing transitions between the moderate and the severe states thereafter, would be more appropriate, please could this be described as a "preferred assumption" rather than a "correction".	The revised model provided in response to the clarification questions did not include the ERG-stated assumption. Patients who discontinued active treatment with mild / resolved sialorrhoea were modelled explicitly according to the transition probabilities for the SoC alone arm of the model (since they were only receiving SoC), with an equal chance of moving from the mild / resolved to mild / resolved, moderate and severe health states for the remainder of the time horizon.	The ERG notes that without a continuity correction factor added all patients who discontinued in the mild state would remain there. However, acknowledges that this wasn't the case in the company's base case. We have added additional text to clarify the point being made. The header of 4.4.4 has been changed to 'Amending the modelling assumption….'

Section 2: Other comments

Issue 1 Misreporting from the submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 40. *"The company performed supplementary searches in several international HTA agencies (NICE, SMC and AWMSG) and health utilities databases (The Cost-Effectiveness Analysis Registry by Tufts Medical Center, the University of Sheffield Health Utilities Database, and the EQ-5D publications database.* ***The searches covered the period up to October 2016.****"*	This sentence in bold is incorrect. The supplementary searches were conducted in September 2018, and therefore covered the period up to this date. The sentence should be amended to say: **The searches covered the period up to September 2018.**	Accurate reporting of the SLR methodology.	Text changed as proposed.

Issue 2 Inaccurate reporting of sensitivity analysis methodology

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 42. *"The first change was fixing the acquisition costs of CBTA, with the second change utilising the standard error of the mean to estimate the uncertainty in NHS reference costs"*	This statement is factually inaccurate, and should be amended as follows: *"The first change was fixing the acquisition costs of CBTA, with the second change utilising the lower and upper quartiles of NHS reference costs to calculate confidence intervals and standard deviation in order to estimate uncertainty"*	Accurate reporting of sensitivity analysis methodology.	We have changed the text as proposed, although in reviewing the method used by the company the ERG has identified what we believe is an error that will overestimate the uncertainty. We believe that the standard error of the mean should be used rather than the standard deviation. The ERG's

			probabilistic base case has been amended accordingly with the uncertainty in the results reduced.

Issue 3 Misreporting from the submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 45. *"the company undertook a scenario analysis using a standardised mortality ratio (SMR) of **1.92** based on a value for patients with Parkinson's disease"*	As highlighted by the ERG in the clarification questions, the value of the SMR reported in Hobson *et al.* is reported to be **1.82**. Merz presented a scenario analysis using this value in their response.	Accurate reporting of scenario analysis.	Text changed as proposed.

Issue 4 Lack of clarity hindering factual accuracy check

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 47. In relation to the Chang *et. al* study, the paragraph ends with the following sentence, which we feel is associated with a lack of clarity. *"As such, changing the severity of the sialorrhoea would not necessarily increase the utility to the level of a patient with a less severe underlying condition."*	We are unable to follow this statement completely, and would be grateful if the sentence could be expanded upon to detail exactly what the ERG mean when they describe *"changing the severity of sialorrhoea"*	Clarity in reporting to enable factual accuracy check.	Additional text has been added to aid understanding.

Issue 5 Misreporting from the submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 49. *"The company assumes two speech pathology or occupational therapy consultations for patients with 'severe' sialorrhoea per 16-week cycle"*	This statement is not clear, and thus should be amended as follows: *"The company assumes one speech pathology consultation and one occupational therapy consultation for patients with 'severe' sialorrhoea per 16-week cycle"*	Accurate reporting of disease management costs.	Text changed as proposed.

Issue 6 Clarity of Markov trace graphs

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 51. The Markov trace graphs presented on page 51 show the percentages of the modelled cohort in the sialorrhoea severity health states for on-treatment and discontinued patients combined.	Please add a footnote to the Markov trace graphs to highlight that the traces for the severity-based health states include both on-treatment and discontinued patients.	Clarity of Markov trace graphs.	We believe it is clear that these traces are just depicting severity states and do not think that the graph is unclear

Issue 7 Clarity of sensitivity analysis methodology

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 52. "*Accordingly the ERG reported these values in terms of net monetary benefit (NMB) 26 assuming a cost per QALY gained threshold of £20,000 and produced Figure 6 and Figure 7*	The NICE guide to the methods of technology appraisal state that NMB should be presented assuming a cost per QALY gained threshold of £20,000 **and £30,000** (Section 5.1.13).[4] As such, the ERG should also present tornado plots for analyses using the £30,000 threshold	This clarification should be included to aid understanding of the sensitivity analysis with respect to the NICE's guide to the methods of technology appraisal.[4]	Figures 6 and 7 have been amended to reflect both ICER thresholds.

for CBTA + SoC versus. glycopyrronium bromide + SoC and CBTA + SoC versus SoC alone respectively"	or acknowledge that the more conservative threshold has been used in the sensitivity analysis.		

Issue 8 Interpretation of resource use associated with different levels of sialorrhoea

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 61. *"ERG believes it plausible that these consultations are not solely for sialorrhoea management, and that they also help in the management of the underlying condition and have therefore explored the impact of this assumption on the ICER"*	Merz believe that this statement misinterprets the sialorrhoea-related resource use in the model, and the report should be amended such that it notes the company's description in the original submission, i.e. that the resource use included in the model represents "sialorrhoea-specific resource use", which is additional to any resource use due to underlying conditions. If this clarification regarding what the resource use included by Merz represents influences the rationale for the ERG's exploratory analysis, then the inclusion of this statement should be considered accordingly.	The Merz model assumed that resource use for underlying conditions does not differ according to sialorrhoea severity, and thus effectively cancels out across the severity states. The resource use included in the model therefore solely represents differences in management due to differences in sialorrhoea severity (i.e. "sialorrhoea-specific resource use", as described in Section B.3.5.2 of the company submission). As we understand it, the ERG analysis that equalises resource use across health states appears to be founded on an assumption that the resource use modelled by Merz is related to the underlying condition and is not sialorrhoea-specific, as equalising sialorrhoea-specific resource use does not appear to be coherent. We propose inclusion of a reference to the company's	Text has been added to page 49 to make it clear that the company are including sialorrhoea costs only. The text on p62 has been amended to consider this too.

		description of resource use as it is important that the reader understands the context of what the company reports resource use to represent in the model, in order to then form a judgement on the ERG's proposed exploratory analysis.	

Issue 9 Inaccurate reporting of utility values

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 62. Table 20. For "Company's model 1", the mean utility value for the "Moderate" health state is reported to be **0.5847**, and the difference compared with the mild state is **0.0372**.	Merz recalculated the utility values for Model 1, finding that the value for the moderate health state was **0.5882**, and the difference compared with the mild state was **0.0337**. The values for the mild / resolved and severe health states were corroborated. Please review this analysis and amend accordingly to ensure these values are correct.	Accurate reporting of utility values. We suspect that the cited utility values are based on summation of predictions across DSFS scores 4-7 rather than 4-6.	The text has been amended as suggested.

Issue 10 Clarity of continuity correction methodology

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 63. *"The ERG assumed that it was not possible for patients receiving SoC only to transition to a resolved / mild health state given that they had chronic, troublesome sialorrhoea,*	The ERG's statement is unclear. Please consider amending as follows: "*The ERG assumed that it was not possible for patients receiving SoC only to transition to a resolved / mild health state given that they had chronic, troublesome sialorrhoea, meaning that*	Clarity of continuity correction methodology.	The text has been amended as suggested

*meaning that a **half of a patient was added to each cell in the SoC transition matrix**"*	*a **half of a patient was added to the remaining transitions from the severe and moderate health states in the SoC transition matrix**"*		

Issue 11 Clarity of threshold analysis methodology

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 69. *"a threshold analysis was undertaken which increased the utility difference between the resolved/mild health state and the moderate health state and increased the utility difference between the moderate health state and the severe health state by a common factor"*	The ERG's statement is not clear. Please consider amending as follows: "*a threshold analysis was undertaken which increased the utility differences (based on the ERG's LCMM analysis) between the resolved / mild health state and the moderate health state and between the moderate health state and the severe health state by a common factor*"	Clarity of threshold analysis methodology.	The text has been changed as proposed

Issue 12 Clarity of threshold analysis methodology

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 69. *"This factor was increased until the ICER of CBTA + SoC compared with SoC was equal to £20,000 per QALY gained"*	The NICE guide to the methods of technology appraisal refer to a range of £20,000-£30,000 (Section 6.3.4).[4] As such, the choice of a £20,000 threshold in the threshold analysis represents the most conservative threshold for exploring cost-effectiveness. This should be acknowledged in the ERG report.	This clarification should be included to aid understanding of the threshold analysis with respect to the NICE's guide to the methods of technology appraisal.[4]	The analyses have been replicated using the £30,000 threshold as well as £20,000.

Section 3: Confidentiality highlighting amendments

Issue 13 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 28. *"At four weeks' follow-up of the SIAXI MP (CS Section B.2.6.1), there was a statistically significant (p=0.004) greater reduction in uSFR for the CBTA 100U group (LS mean change -0.13) compared with the PBO group (LS mean change -0.04) (Table 8)."*	Confidentiality highlighting can be removed in this sentence. Details of the LS mean change in uSFR have been published by Jost *et al.* 2018 and therefore do not need to be highlighted as confidential.	Correction to confidentiality highlighting.	Highlighting removed as suggested and also in Section 1.2 p7

Issue 14 Confidentiality highlighting amendment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 30 Table 8. All of the data pertaining to the LS-mean change in uSFR does not need to be highlighted as confidential (see below).	Details of the LS mean change in uSFR have been published by Jost *et al.* 2018 and therefore do not need to be highlighted as confidential.	Correction to confidentiality highlighting.	Highlighting removed as suggested.

Mean change from baseline to Week 4				
Mean change (SD)	73	-0.12 (0.21)	36	-0.03 (0.21)
LS-Mean change (SE) (95% CI) [5]	73	-0.13 (0.026) (-0.18; -0.08)	36	-0.04 (0.033) (-0.11; 0.03)

LS-Mean change difference versus placebo (95% CI) [5, 6]	73	-0.09 (0.031) (-0.15; -0.03)	-	-
p-value (versus placebo)		0.004	-	-
Mean change from baseline to Week 8				
LS-Mean change (SE) (95% CI) [5]	73	-0.13 (0.026), (-0.19; -0.08)	36	-0.02 (0.033), (-0.08; 0.05)
LS-Mean change difference versus placebo (95% CI)	73	-0.12 (0.030), (-0.18; -0.06)		
p-value (versus placebo)		≤0.001		
Mean change from baseline to Week 12				
LS-Mean change (SE) (95% CI) [5]	73	-0.12 (0.026), (-0.17; -0.07)	36	-0.03 (0.033), (-0.09; 0.04)

LS-Mean change difference versus placebo (95% CI)	73	-0.09 (0.031), (-0.15; -0.03)					
p-value (versus placebo)		0.004					
Mean change from baseline to Week 16							
LS-Mean change (SE) (95% CI)	73	-0.11 (0.027), (-0.17; -0.06)	36	-0.01 (0.035), (-0.08; 0.06)			
LS-Mean change difference versus placebo (95% CI)	73	-0.10 (0.033), (-0.17; -0.04)					
p-value (versus placebo)		0.002					

Section 4: Typographical errors

Issue 15 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 42. *"This was not a change that could not be made by the ERG whilst assuming that patients on SoC could not become mild / resolved and was thus not enacted"*	Merz believe that this statement contains a typographical error and should read as follows: *"This was not a change that could ~~not~~ be made by the ERG whilst assuming that patients on SoC could not become mild / resolved and was thus not enacted"*	This statement should not contain a double negative.	The sentence has been amended as suggested.

References

1. Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis. : John Wiley & Sons Inc., 2004.
2. Bhat HS, Kumar N. On the derivation of the Bayesian Information Criterion. School of Natural Sciences, University of California 2010.
3. Jones RH. Bayesian information criterion for longitudinal and clustered data. Statistics in medicine 2011;30:3050-3056.
4. National Institute for Health and Care Excellence (NICE). PMG9: Guide to the methods of technology appraisal. Available at: https://www.nice.org.uk/process/pmg9/chapter/foreword [Last accessed: 1st May 2019].
5. ClinicalTrials.gov. Clinical Study to Investigate the Efficacy and Safety of Two Dose Levels of NT 201 Versus Placebo in Treating Chronic Troublesome Sialorrhea in Various Neurological Conditions. Available at: https://clinicaltrials.gov/show/nct02091739 [Last accessed: 07 January 2019], 2014.
6. Merz. SIAXI Interim Clinical Study Report (16th May 2017).

NICE National Institute for Health and Care Excellence

Technical engagement response form

Clostridium Botulinum toxin A for treating chronic sialorrhoea [ID1150]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **21st June 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- 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. If confidential information is submitted, please also send a second version of

your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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

Your name	**Louis Constandinos**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Merz Pharma UK Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Questions for engagement

Issue 1a: Comparators	
What active treatments are used to treat sialorrhoea in NHS clinical practice? Does it vary by the underlying aetiology?	• Based on feedback from UK clinical experts, the active treatments used to treat sialorrhoea in NHS clinical practice align with the NICE clinical guidelines for the management of several neurological conditions, including Parkinson's disease in adults (NG71, July 2017), cerebral palsy in under 25s (NG62, August 2016) and motor neurone disease (NG42, September 2015).[1-3] • Both NG62 and NG42 state that unlicensed anticholinergic therapies, such as glycopyrrolate (glycopyrronium bromide) and transdermal hyoscine hydrobromide, should be considered for the first-line pharmacological management of sialorrhoea.[1-3] The Parkinson's disease (NG71) guidelines recommend that pharmacological management of drooling should only be considered if non-pharmacological management (e.g. speech and language therapy) is not available or has not been effective, and that glycopyrronium bromide should be considered to manage drooling of saliva in people with Parkinson's disease. No anticholinergic therapies currently hold a licence for the treatment of sialorrhoea. • If treatment for drooling of saliva with anticholinergic therapies is not effective, not tolerated or contraindicated (for example, in people with cognitive impairment, hallucinations or delusions, or a history of adverse effects following anticholinergic treatment), all three guidelines currently recommend clinicians to consider referral to a specialist service for botulinum toxin A.[1-3] • Feedback from UK clinical experts aligns with the above; patients with mild/moderate chronic sialorrhoea are first managed with basic non-pharmacological management, which may include practical aids, such as bibs, as well as speech, language and occupational therapy.[4] • For patients in whom non-pharmacological management is inadequate at controlling their sialorrhoea, anticholinergic therapies are the first choice in terms of active therapy. Oral glycopyrronium bromide is one of the most commonly prescribed active treatments, and transdermal hyoscine hydrobromide or sublingual atropine sulfate are also used in some patients.

	Treatment choice is currently heterogenous, reflecting that anticholinergic treatment options are unlicensed in adult patients with siallorhea. • For patients in whom anticholinergic therapies are not effective, some patients may currently receive treatment with off-licence Xeomin. • In current clinical practice, the choice of active treatment does not vary significantly by aetiology, but may depend on underlying co-morbidities, the adverse event profile of the therapies available, as well as other factors including clinician and patient choice. When considering the sequelae of a particular disease in combination with the adverse effect profile of a specific pharmacotherapeutic intervention there is variation in treatment choice. Current NICE guidelines for Parkinson's disease (NG71), for example, recommend that patients contraindicated for glycopyrronium bromide, due to specific sequelae of Parkinson's disease, be considered for referral to specialist services for treatment with clostridium botulinum toxin serotype A.[1] • The FDA, EMA, and MHRA have all granted broad licences for Xeomin, that specify that Xeomin is indicated for the treatment of chronic sialorrhea due to neurological disorders in adults, regardless of specific aetiologies.[5] • The mechanism of action, and mode of delivery, of Xeomin means it is a focal treatment that both avoids the polypharmacy so prevalent in the treatment of patients with neurological disorders, and the broader, more deleterious adverse event profiles associated with systemic treatments like the anticholinergic therapies.
Is the company's positioning of CBTA appropriate for all neurological conditions associated with sialorrhoea?	• NICE clinical guidelines currently recommend consideration of referral to a specialist service for botulinum toxin A if treatment for drooling of saliva with unlicensed anticholinergic therapies is not effective, not tolerated or contraindicated (for example, in people with cognitive impairment, hallucinations or delusions, or a history of adverse effects following anticholinergic treatment) i.e. in second-line following treatment with anticholinergic therapies. • Merz is positioning Xeomin as a first-line active treatment option for chronic sialorrhoea due to neurological disorders in adult patients where non-pharmacological management is inadequate. Xeomin is positioned as appropriate for chronic sialorrhoea due to all neurological conditions, in line with its licence, as the mechanism of action of Xeomin is such that the treatment effect is

	independent of the aetiology of sialorrhoea • This positioning is consistent with the FDA, EMA, and MHRA provision of broad licences for Xeomin as a treatment for chronic sialorrhoea due to neurological disorders in adult patients, regardless of aetiology. • Xeomin is the first, and currently only, licensed treatment for chronic sialorrhoea due to neurological disorders in adult patients. We believe this, in addition to the advantages of Xeomin's mechanism of action, mode of administration and the breadth of its licence to include any aetiology, supports the proposed positioning of Xeomin, which would provide clinicians and patients with the valuable choice of an alternative therapy to unlicensed anticholinergics for patients requiring active treatment.
Issue 1b: Treatment choice	
What factors affect the decision on whether active treatment is preferred over standard of care? In particular: • Does the decision change based on underlying neurological condition that causes sialorrhoea? • Does the decision change based on severity of sialorrhoea? Is severe sialorrhoea a distinct subgroup from moderate sialorrhoea?	• The decision on whether active treatment is preferred over standard of care would not typically differ based on the underlying cause of a specific neurological disorder. The choice of whether an active treatment is required in addition to standard of care (i.e. non-pharmacological management of chronic sialorrhoea) is dependent on the sialorrhoea severity, sequalae of the particular neurological disorder, underlying co-morbidities, as well as other factors including clinician and patient choice • For patients with mild sialorrhoea only, non-pharmacological management (standard of care) may be sufficient • For patients with moderate or severe sialorrhoea, non-pharmacological management is unlikely to be sufficient and active treatment, currently with unlicensed anticholinergic therapies, will likely be tried. • Severe sialorrhoea is not necessarily a distinct subgroup from moderate sialorrhea; clinicians may use different measures to determine the severity of sialorrhoea. It should be noted that although used to define health states within the company's economic model, the drooling severity and frequency score (DSFS) scale is a continuous scale and is therefore not definitively split into distinct groups in clinical practice.

What factors affect the decision to discontinue active treatment? In particular: • Will any rules be used to assess whether CBTA is stopped? • If CBTA was available as a first-line treatment, how would this affect the pathway? Would anticholinergics still be considered first?	• Feedback from UK clinical experts sought by Merz stated that the decision to discontinue active treatment with Xeomin would typically be based on patient/clinician preference, the experience of adverse events, contraindications or a lack of efficacy • Whilst it is acknowledged that clinicians are unlikely to persist with treatment if it were perceived not to be beneficial based on the length of time a patient had gone without responding to treatment, there are no formal stopping rules associated with the use of Xeomin. Some clinicians may choose to stop treatment with Xeomin after two injection cycles if there were no perceived benefit • There is no evidence to suggest that the development of immunity to Xeomin would be a cause for concern. Data available to Merz demonstrate that no treatment-naïve Xeomin patient has been observed to develop secondary loss of response due to the formation of neutralising antibodies. This has been demonstrated in over 2 million treatment episodes, including all Xeomin clinical trials, real world studies, and, to date, in 12 years of post-marketing PV surveillance. This is also supported by preclinical immunological studies. [6] • NICE clinical guidelines currently recommend the use of unlicensed anticholinergic therapies as the first-line management of chronic sialorrhoea with active pharmacological therapy. If recommended, Xeomin would provide an alternative first-line treatment choice to clinicians who deem their patient to require active pharmacological management. In doing so, it would provide clinicians with an active pharmacological treatment option that is licensed for this indication, and supported by a robust clinical evidence base. This would be valuable in the context of current treatment options (anticholinergics) being unlicensed, unsupported by a robust clinical evidence base and associated with undesirable side effect profiles. It would also be expected to provide benefits in terms of helping reduce treatment heterogeneity/polypharmacy that arises as a result of the lack of a licensed therapy option. Furthermore, based on the company analyses and as per the NICE technical team's stated preferred analysis, the choice of Xeomin in place of anticholinergics by clinicians would represent a cost-effective use of NHS resources. • There may be cases where patient or clinician preference means that anticholinergics would still represent the preferred first-line active pharmacological treatment option. In such cases, Xeomin would provide a second active pharmacological treatment option should treatment with

	anticholinergics be unsuccessful in adequately managing sialorrhoea symptoms and clinicians deem that trying a second active treatment is preferable to consigning patients to best supportive care alone.
Issue 2: Outcomes	
What outcome measures are appropriate for measuring sialorrhoea?	• The outcome measures used to assess the severity of sialorrhoea in clinical practice may vary, depending on the underlying aetiology. • Given the heterogeneity in underlying aetiologies in the SIAXI trial the outcome measures in the SIAXI trial represent global outcome measures for the assessment of sialorrhoea for all aetiologies (i.e. they are not aetiology-specific): unstimulated salivary flow rate (uSFR), Patient's Global Impression of Change Scale (GICS), and Drooling Severity and Frequency Scale (DSFS) • Control of salivation severity and frequency is a key goal in the treatment of sialorrhoea, and therefore, the outcome measures evaluated in the SIAXI trial are considered relevant to both patients and clinicians. • uSFR was a primary outcome in the SIAXI trial. uSFR is a reproducible, objective, and easy to use method, which represents a direct measure of saliva production, thus serving as a robust indicator of symptomatic improvement • DSFS was a key secondary outcome in the SIAXI trial. Based on expert clinician feedback sought by Merz to inform the development of the economic model, DSFS was deemed to be the most clinically relevant measure of sialorrhea disease severity. Additionally, DSFS has been categorised as a 'suggested' symptom-based scale for evaluating sialorrhoea and is subsequently widely implemented in this setting. The DSFS is a subjective scale which correlates well with the disease burden associated with sialorrhoea
Issue 3a: Health related quality of life (EQ-5D-3L	
Which symptoms associated with sialorrhoea have the highest impact on quality of life?	• There is an absence of data on which symptoms of sialorrhoea have the highest impact on health-related quality of life (HRQoL) • Chronic sialorrhoea is associated with perioral dermatitis, eating and speaking difficulty, bad

	breath, sleep disturbance, dehydration and fatigue, all of which negatively impact upon HRQoL. Furthermore, sialorrhoea can have a considerable psychosocial impact on patients through social embarrassment and decreased self-esteem, which can lead to social isolation and clinical depression. • Posterior loss of control of saliva is also associated with morbidity and mortality due to aspiration pneumonia and chest infections. There is a demonstrable association, both in the published literature and based on clinical knowledge, between poor salivary control and aspiration pneumonia/chest infection.[7, 8] Taking Parkinson's disease as the example, the most common presentation to A&E by patients with advanced Parkinson's disease is for chest infection.[9, 10] Feedback from clinicians has specifically mentioned that sialorrhoea is an underlying cause for aspiration of saliva, and hence chest infections. This associated morbidity and mortality has cost implications for the NHS in terms of high-dependency unit beds/treatment of acute infection etc, and an obviously serious impact on HRQoL for patients. • Patients with neurological conditions are already relatively vulnerable to confusion, disorientation, and falls. The adverse event profiles of commonly used anticholinergic therapies pose a risk of exacerbating these issues. In contrast, the adverse event profile of Xeomin compares favourably in that its focal action does not exacerbate these existing issues. In this regard, Xeomin would be expected to provide HRQoL benefits, and a reduction in hidden costs of complications to the NHS, when compared to anticholinergic therapies. • Finally, chronic sialorrhoea can also increase the burden on caregivers who may already be supporting the patient in managing the severe consequences of neurological disease; this can lead to depression and anxiety, and consequent reductions in caregiver quality of life which are not captured within the cost-effectiveness analysis for this submission.
Is the EQ-5D-3L questionnaire used in the SIAXI trial sensitive to health-related quality of life changes associated with freedom from sialorrhoea?	• Generic HRQoL instruments such as the EQ-5D have been shown to be insensitive to changes in disease severity in a number of disorders, particularly those that are neither painful nor life-threatening, which likely applies to sialorrhoea. Although not the same indication, a previous study in a neurological indication (supranuclear palsy) has reported that the EQ-5D was found to be insensitive to addressing patient issues that included dysphagia (which overlaps with some of the quality of life impacts of sialorrhoea with regards to difficulty swallowing and potential challenges

	with eating and drinking).[11] • The impact of sialorrhoea on patient HRQoL is varied and potentially substantial, as described above. Improvements in sialorrhoea severity may affect many aspects of HRQoL that are covered by the EQ-5D questionnaire. However, the vast majority of patients with sialorrhoea also suffer from extremely debilitating underlying conditions which themselves have a detrimental impact on HRQoL, including Parkinson's disease, motor neurone disease, stroke or cerebral palsy, traumatic or acquired brain injury. Therefore, whilst improvements in sialorrhoea severity are associated with meaningful HRQoL benefits for patients, measurement of these HRQoL benefits is challenging and complex in the context of severe underlying neurological diseases of varying aetiology that have their own dynamic impacts on patient HRQoL. As such, HRQoL impacts of sialorrhoea improvement may not be well captured by the EQ-5D-3L scoring system. • By way of example, depression is one of the sequelae of Parkinson's disease, arising from bioneurological disruption and abnormalities of dopamine signalling. Parkinson's patients may also suffer from sialorrhoea, which may have a sufficient additional negative impact on depression (and hence HRQoL) through its effects on patient self-esteem, levels of social embarrassment and ability to sleep. Generic, non-specific HRQoL measures are likely unable to reflect the underlying complexity of measuring HRQoL in such contexts; by capturing overall HRQoL status, they are not sensitive to the impact of improvements in sialorrhoea on HRQoL against a background of changes in HRQoL that may arise dynamically over time due to developments (positive and negative) in underlying aetiology. Change in disease state and impact (measured by DSFS and GICS) are more appropriate measures of HRQoL in this case than the EQ-5D-3L. Data for these outcomes from the SIAXI trial demonstrated treatment with Xeomin to be associated with statistically significant improvements in both DSFS and GICS versus best supportive care. • Furthermore, the EQ-5D-3L measure will only register a change in patient utility where a patient is able to indicate a step-change in the level of at least one domain, e.g. in terms of allowing the patient to move from a 3 (extreme problems) to a 2 (some problems), or from a 2 (some problems) to a 1 (no problems). Taking an example, the majority of patients enrolled within the SIAXI trial responded with a score of 2 (some problems) for all 5 domains at baseline (mobility: 70%; self-care: 51%; usual activities: 59%; pain: 64%; anxiety/depression: 42%). For an improvement in HRQoL due to reduced drooling to register on the EQ-5D-3L, such patients would need to feel able

	to grade these domains with a score of 1 (no problems). • Given the impact of their severe underlying conditions on HRQoL, many trial patients will have been highly unlikely to be able to describe "no problems" for many or all of the domains. Nevertheless, there is no doubt that improvements in sialorrhoea severity do have a positive impact on patient HRQoL, as indicated by the results of the patient's Global Impression of Change Scale (GICS) from the SIAXI trial (the LS-Mean difference between the Xeomin 100 U group and placebo group was 0.58 [SE: 0.183], representing a statistically significant difference in GICS scores between these groups [p=0.002]), and as implied by the fact that clinicians and patients currently choose active treatment for their sialorrhea with anticholinergic treatments in clinical practice, despite these treatments being unlicensed.
Are the EQ-5D-3L results from the SIAXI trial generalisable to the entire population of people with sialorrhoea?	• There are no issues regarding the generalisability of the data from the SIAXI trial to the entire population of patients with sialorrhoea. As highlighted previously, the mechanism of action of Xeomin is such that the treatment effect is both focal, and independent of the aetiology of sialorrhoea. Feedback from UK clinical experts strongly indicated that the efficacy of Xeomin would be generalisable regardless of aetiology • However, and as highlighted in the company submission, whilst considered *generalisable* to the entire population of patients with sialorrhoea, the EQ-5D-3L results from the SIAXI trial are not considered to reflect clinically plausible changes in HRQoL associated with improvements in sialorrhoea severity. The EQ-5D results do not align with the other clinical efficacy results of the trial, that demonstrate Xeomin to have a statistically significant impact on patient salivary rate and sialorrhoea severity, in terms of uSFR, DSFS as well as HRQoL as measured via the GICS score. The reasons for this misalignment have been described above, and are considered to be reflective of the insensitivity of the EQ-5D-3L measure to improvements in sialorrhoea severity.
Issue 3b: Utility values	
What are the most appropriate utility values for people with sialorrhoea?	• No relevant utility data for the population of interest were identified in a systematic literature review conducted to inform the health state utility values for the cost-effectiveness model • Therefore, utility values for each severity-based health state were derived from an analysis of patient-level EQ-5D-3L scores versus DSFS scores from the SIAXI trial. The results of the model

	predicted a difference of only 0.0423 and 0.0543 between the utility of mild/resolved versus moderate and the mild/resolved versus severe health states, respectively. As such, the resulting health state utility values were not considered to appropriately reflect the differences in HRQoL expected given the differences in sialorrhoea severity • Consequently, an alternative approach was adopted, using health state utilities for a set of drooling severity health states reported in a cost-effectiveness analysis conducted by the NG62 guidelines for cerebral palsy in under 25s. Due to a lack of evidence, the health state utility values were hypothetical, and based on rationalisation of the expected potential impact of drooling severity on QoL. These utilities set a base case disutility per unit increase in drooling severity score set to a value of 0.025. This resulted in a difference in utility of 0.2 between the least and most severe drooling health states, which was considered to be clinically plausible • It is acknowledged that neither set of utility values can be considered fully appropriate; both sets of utility values are associated with substantial uncertainty. There is also a lack of relevant, published data in this indication to aid decision-making. Given the limitations in defining empirical estimates of health state utilities, the most appropriate utility values for use in the model should be those that are deemed to be the most clinically plausible and therefore applicable to clinical practice. A difference of only 0.0423 and 0.0543 between the utility of mild/resolved versus moderate and the mild/resolved versus severe health states is not clinically plausible. Therefore, whilst we acknowledge the limitations in the utilities estimated from the NG62 guidelines and that the "true" utility values likely lie somewhere between those measured in the trial and those from NG62, on balance we consider that the values derived from the NG62 guidelines should be deemed to be the more appropriate utility values to use in this context.
Which of the company or ERG models uses the most plausible utility values?	• As highlighted above, the ERG-chosen utility values derived from the EQ-5D data of the SIAXI trial do not have face validity or reflect the improvement in HRQoL associated with an improvement in sialorrhoea severity. • The company utility values are therefore considered to be the more clinically plausible hence their use within the company base case analysis. It is acknowledged that these utility values are associated with unavoidable uncertainty; however, it is reasonable to assume that a difference in utility between the mild/resolved health state and the severe health state of less than 0.062 would

	not be reflective of the differences in utility expected with such an improvement in sialorrhoea severity in clinical practice. The difference is likely to be much greater than this, as adopted within the base case analysis.
What is the expected utility value gain associated with freedom from severe sialorrhoea?	• There are very limited data available to indicate the expected utility value gain associated with freedom from severe sialorrhoea • As stated in NICE CG62, and in our submission, drooling can significantly impact a person's health by increasing the risk of infection and risk of choking, as well as a number of facets of quality of life; in social participation, communication, self-esteem, eating and swallowing. • The threshold analysis conducted as part of our submission highlighted that, for Xeomin to not represent a cost-effective use of NHS resources (assuming a £30,000 per QALY threshold), the difference in utility between the mild/resolved health state and the severe health state, assuming all other assumptions in the base case hold, would need to be less than 0.062. The difference is likely to be much greater than this in UK clinical practice. • Due to the lack of empirical data on sialorrhoea it is challenging to estimate the potential utility impact of addressing aspects of quality of life such as those mentioned above. A non-systematic search finds that dysphagia, which would be associated with some of the same challenges as sialorrhoea in terms of difficulty swallowing, or choking when eating or drinking has previously been reported to be associated with a disutility of 0.04802 when modelled as an adverse event in a previous NICE appraisal.[12] Dysphagia by no means conveys the extent of the quality of life impacts of sialorrhoea, as it would not capture impacts of sialorrhoea on self-esteem and confidence, likely does not pose the same impacts in terms of sleep disruption, does not carry the same risks of clinical events such as aspiration pneumonia and does not have the same potential to result in social isolation and depression as its impacts are markedly less visible. Given these differences, along with other methodological limitations in assuming this disutility translates to the current setting, we absolutely do not support the use of a dysphagia disutility as a proxy for modelling the quality of life impact of sialorrhoea. However, we note this disutility in order to demonstrate the extent to which some (and by no means all) of the quality of life impacts of sialorrhoea may have been considered to impact on utility in other contexts.

Issue 4: Ultrasound guidance	
In clinical practice, would 100% of CBTA procedures include the use of ultrasound imaging?	• According to feedback from UK clinical experts sought by Merz, ultrasound guidance is used variably for Xeomin administration in UK clinical practice • Consequently, the proportion of patients modelled to receive an ultrasound to guide Xeomin administration in our submission was based on the proportion of patients who received ultrasound guidance in the SIAXI trial • It should be noted that the assumption of 100% of Xeomin procedures using ultrasound imaging has limited impact on the cost-effectiveness results for Xeomin and, at the same time, does not take into account any improved efficacy that may be achieved from the use of ultrasound imaging in 100% of patients, given that fewer than 100% of patients received ultrasound imaging in the SIAXI study
Issue 5: Implementation	
Are there any additional NHS resources required for treatment with CBTA? In particular: • Will clinicians require further training to administer CBTA injections? • Where is CBTA treatment currently provided in the NHS (specialist or non-specialist centres)? Is this likely to change if CBTA is recommended for sialorrhoea?	• Xeomin treatment is currently provided in specialist centres throughout the UK; the administration of Xeomin in specialist centres is not likely to change following the recommendation of Xeomin for sialorrhoea • The current state of clinical practice varies considerably, with some specialist centres having dedicated sialorrhoea clinics, and some absorbing the treatment of sialorrhoea into existing neurology appointments. • Training to inject Xeomin to treat chronic sialorrhoea is necessary, but given the results from SIAXI which showed that there was no significant difference in safety between injection using ultrasound localisation and anatomical correlate localisation of the gland, the accessibility of the glands as injection sites (c.f. muscles in cervical dystonia, for example), and the straightforward dosing regimen for Xeomin, the complexity and length of this training is not onerous. • Xeomin is injected for all licenced indications by a wide variety of healthcare professionals including neurologists, neurorehabilitation physicians (physiatrists), speech and language professionals, ENT surgeons, physiotherapists, and nurses, all under the guidelines and

	regulations appropriate for their respective roles. We do not anticipate that a significant additional resource will be required for the treatment of chronic sialorrhoea with Xeomin as, on an individual centre/trust basis, the clinical pathways can be developed/adapted to accommodate treatment accordingly. • Additionally, as delineated above, we expect that there will be a reduction in overall resource requirement by treating chronic sialorrhoea with Xeomin as it is dominant in regards to glycopyrronium bromide, has a superior side effect profile to the anticholinergic therapies as a general class (especially in the populations most likely to require treatment),[13] and is likely to reduce hospital admissions for chest infection/aspiration pneumonia based on both literature data and reports by clinicians[4, 9, 10, 14]

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Clostridium Botulinum toxin A for treating chronic sialorrhoea [ID1150]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **21st June 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- 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. If confidential information is submitted, please also send a second version of

your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Association of British Neurologists (ABN) Movement Disorders Advisory Group**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1a: Comparators	
What active treatments are used to treat sialorrhoea in NHS clinical practice? Does it vary by the underlying aetiology?	1. Oral anticholinergics, either acting systemically or locally, without variation according to aetiology. Of note, whilst atropine and glycopyronium drops are frequently used in clinical practice, they are actually not licensed for this indication in PD.
Is the company's positioning of CBTA appropriate for all neurological conditions associated with sialorrhoea?	We can only comment on PD and related movement disorders

Issue 1b: Treatment choice	
What factors affect the decision on whether active treatment is preferred over standard of care? In particular: • Does the decision change based on underlying neurological condition that causes sialorrhoea? • Does the decision change based on severity of sialorrhoea? Is severe sialorrhoea a distinct subgroup from moderate sialorrhoea?	Our comments are only with regards to PD and related movement disorders. The decision change is based on the following: 1. Subjective and objective severity of sialorrhoea 2. Effectivity of previous treatment 3. Suitability of individual patient for standard treatment vs CBTA 4. The severity of sialorhoea can fluctuate, there is a continuum from mild to moderate to severe
What factors affect the decision to discontinue active treatment? In particular: • Will any rules be used to assess whether CBTA is stopped? • If CBTA was available as a first-line treatment, how would this affect the pathway? Would anticholinergics still be considered first?	1. Lack of efficacy 2. Side effects, in particular impaired swallowing 3. Anticholinergics are not ideal in many PD patients due to adverse cognitive effects, so for many PD patients a local targeted treatment may be preferable. Anticholinergics have poor long-term tolerability. However, a small number of patients with PD may already be on anticholinergics for their motor symptoms. 4. (Some patients may respond better to Botulinum toxin B)
Issue 2: Outcomes	
What outcome measures are appropriate for measuring sialorrhoea?	1. Detailed history from patient and spouse/carers 2. Physical examination 3. Scoring systems are not part of standard clinical practice

Issue 3a: Health related quality of life (EQ-5D-3L	
Which symptoms associated with sialorrhoea have the highest impact on quality of life?	Saliva production and associated embarrassment, skin irritation, hygiene issues, etc
Is the EQ-5D-3L questionnaire used in the SIAXI trial sensitive to health-related quality of life changes associated with freedom from sialorrhoea?	It is unlikely that any of the very specific consequences of sialorrhoea or the effect of CBTA on it would have been reliably detected in a non-saliva specific questionnaire
Are the EQ-5D-3L results from the SIAXI trial generalisable to the entire population of people with sialorrhoea?	See above
Issue 3b: Utility values	
What are the most appropriate utility values for people with sialorrhoea?	Reduced saliva production with resulting decrease in reduction of skin irritation, reduced embarrassment, improvement hygiene
Which of the company or ERG models uses the most plausible utility values?	We are not ERG model experts and can therefore not comment on this
What is the expected utility value gain associated with freedom from severe sialorrhoea?	See above

Issue 4: Ultrasound guidance	
In clinical practice, would 100% of CBTA procedures include the use of ultrasound imaging?	No, only a minority of cases would require ultrasound guidance
Issue 5: Implementation	
Are there any additional NHS resources required for treatment with CBTA? In particular: • Will clinicians require further training to administer CBTA injections? • Where is CBTA treatment currently provided in the NHS (specialist or non-specialist centres)? Is this likely to change if CBTA is recommended for sialorrhoea?	Some clinicians may need additional training for CBTA CBTA treatment is currently only provided in secondary and tertiary care. This is unlikely to change if CBTA was to be formally recommended for sialorrhoea

Addendum for the Clostridium botulinum neurotoxin type A for treating chronic sialorrhoea Single Technology Appraisal following a Patient Access Scheme

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK Date completed (02/07/2019)

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 17/156/06.

1 Background

In February 2019, the company submitted to the National Institute for Health and Care Excellence (NICE) the evidence for use of clostridium botulinum toxin A (CBTA) (Xeomin®) in the treatment of chronic sialorrhoea.[1] Following the Technical Engagement step, the company submitted a Patient Access Scheme (PAS) involving a simple discount of [redacted] resulting in an acquisition price of [redacted] for 100U of CBTA compared with the list price of £129.90.

2 Company's cost effectiveness analysis incorporating the PAS

2.1 Summary of evidence submitted

Following the PAS submission, the company presented new base case cost-effectiveness results based on its most recent cost-effectiveness model. Table 1 and Table 2 present the base case results without and with PAS respectively.

Within this section, the ERG reproduces these analyses incorporating the PAS.

Table 1: Company's revised model - base case results (without PAS)

Intervention	Total costs (discounted)	Total LYG (discounted)	Total QALYs (discounted)	Incr. costs	Incr. LYG	Incr. QALYs	ICER for Xeomin versus comparator (£/QALY)
Xeomin plus Soc	£6,103	8.18	3.52	-			
Glycopyrronium bromide plus SoC	£14,966	8.18	3.34	-£8,863	0.00	0.18	Xeomin plus SoC dominant
SoC alone	£3,010	8.18	3.20	£3,093	0.00	0.32	£9,583

Table 2: Company's revised model - base case results (with PAS)

Intervention	Total costs (discounted)	Total LYG	Total QALYs (discounted)	Incr. costs	Incr. LYG	Incr. QALYs	ICER for Xeomin versus comparator (£/QALY)
Xeomin plus Soc	[redacted]	[redacted]	[redacted]			[redacted]	
Glycopyrronium bromide plus SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2.2 Critique of company's approach

Section 4.3.4 of the ERG report provides details of the main issues identified by the critical appraisal conducted by the ERG.[2] This text is not reproduced here for brevity. The ERG's exploratory analyses and base case are provided in Section 3.

3 ERG's cost effectiveness results when incorporating the PAS

The ERG replicated its base case cost effectiveness analysis and exploratory analyses detailed in Section 4.4 of the ERG report incorporating the proposed PAS.[2] As in Section 5 of the ERG report, all results were run deterministically with probabilistic analyses conducted only for the ERG base case. Table 3 and Table 4 presents the exploratory analyses (with PAS) undertaken by the ERG for severe and moderate patients respectively. For completeness, as the Technical Engagement document did not consider disease severity, Table 5 presents the same analyses for the entire patient population.

3.1 Interpreting the deterministic analyses incorporating the PAS

The utility values associated with the severity of sialorrhoea remained the key driver of the ICER for CBTA + standard care (SoC) compared with SoC alone. However, the PAS introduction led to observable decrease in the ICER values associated with the ERG's base case.

For patients with severe sialorrhoea the deterministic ICER of CBTA + SoC compared with SoC alone rose to over [redacted] (compared with over £44,000 at list price) using the utility values generated directly from the SIAXI trial and the ERG's LCMM approach. For moderate patients, this value was above [redacted] (compared with above £50,000 at list price) and was over [redacted] (compared with over £47,000 at list price) in the combined severity patient population.

The ERG's base case ICERs increase if 1) all CBTA injections were guided with ultrasound and there was no increase in effectiveness of treatment and 2) if resource use did not alter based on the severity of sialorrhoea.

CBTA dominated glycopyrronium bromide in all of the analyses undertaken by the ERG.

3.2 ERG base case probabilistic results incorporating the PAS

The ERG performed probabilistic sensitivity analyses (PSA) using 1,000 iterations. Cost-effectiveness acceptability curves and cost-effectiveness planes are presented in Appendix 1. Using the PAS price of CBTA, the ERG base case probabilistic ICER of CBTA + SoC compared with SoC was over [redacted] for severe patients, over [redacted] for moderate patients, and over [redacted] for the overall population (compared with £41,000, £48,000 and £45,000 respectively at list price).

Compared with SoC alone and using the PAS price, the probability of CBTA + SoC being cost-effective at a cost per QALY gained threshold of £20,000 increased to [redacted], [redacted], and [redacted] for severe, moderate and all patients respectively. At a threshold of £30,000, the respective probabilities increased to [redacted], [redacted], and [redacted].

CBTA + SoC was cost-effective in [redacted] of the PSA iterations for both severe and moderate patients compared with glycopyrronium bromide using a cost per QALY gained threshold of £20,000.

Table 3: Exploratory model results for severe patients (with PAS)

Analysis	Discounted costs			Discounted QALYS			ICER (CBTA + SoC versus SoC)
	CBTA + SoC	Glyc Br + SoC	SoC	CBTA + SoC	Glyc Br + SoC	SoC	
Company base case	[redacted]	£15,020	£3,070	[redacted]	3.318	3.175	[redacted]
1) Using the company's LCMM model	[redacted]	£15,020	£3,070	[redacted]	4.914	4.876	[redacted]
2) Applying the ERG's LCMM utility values	[redacted]	£15,020	£3,070	[redacted]	4.875	4.846	[redacted]
3) Correcting CBTA administration costs	[redacted]	£15,020	£3,070	[redacted]	3.318	3.175	[redacted]
4) Severe patients discontinue active treatment after second treatment cycle	[redacted]	£10,693	£3,070	[redacted]	3.268	3.175	[redacted]
5) Mild patients who discontinue active treatment, transition to the moderate health state□	[redacted]	£15,013	£3,070	[redacted]	3.323	3.175	[redacted]
6) Applying the modified correction factor*	[redacted]	£15,108	£3,210	[redacted]	3.287	3.125	[redacted]
7) Adjusting the population's SMR value	[redacted]	£13,146	£2,544	[redacted]	2.732	2.610	[redacted]
8) Correcting the acquisition costs for glycopyrronium bromide	[redacted]	£14,076	£3,070	[redacted]	3.318	3.175	[redacted]
ERG base case (scenarios 2 – 8)	[redacted]	£9,505	£2,661	[redacted]	4.003	3.982	[redacted]
ERG base case (probabilistic results)	[redacted]	£9,324	£2,469	[redacted]	3.698	3.675	[redacted]
ERG base case (using the NG utility values, i.e. excluding scenarios 1 and 2)	[redacted]	£9,505	£2,661	[redacted]	2.673	2.567	[redacted]
9) Assuming all patients require an ultrasound scan for the CBTA injections†	[redacted]	£9,505	£2,661	[redacted]	4.003	3.982	[redacted]
10) Assuming no additional resource use for the different sialorrhoea severity levels†	[redacted]	£7,110	£0	[redacted]	4.003	3.982	[redacted]

□ This produces more QALYs than the base case due to the continuity correction applied in the mild health state * In conjunction with scenario 5 †In conjunction with the ERG base case

CBTA, Clostridium botulinum toxin A; Glyc Br, Glycopyrronium Bromide; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, Standard of Care

Table 4: Exploratory model results for moderate patients (with PAS)

Analysis	Discounted costs			Discounted QALYS			ICER (CBTA + SoC versus SoC)
	CBTA + SoC	Glyc Br + SoC	SoC	CBTA + SoC	Glyc Br + SoC	SoC	
Company base case	[redacted]	£14,900	£2,939	[redacted]	3.371	3.233	[redacted]
1) Using the company's LCMM model	[redacted]	£14,900	£2,939	[redacted]	4.920	4.882	[redacted]
2) Applying the ERG's LCMM utility values	[redacted]	£14,900	£2,939	[redacted]	4.884	4.856	[redacted]
3) Correcting CBTA administration costs	[redacted]	£14,900	£2,939	[redacted]	3.371	3.233	[redacted]
4) Severe patients discontinue active treatment after second treatment cycle	[redacted]	£11,306	£2,939	[redacted]	3.330	3.233	[redacted]
5) Mild patients who discontinue active treatment, transition to the moderate health state□	[redacted]	£14,893	£2,939	[redacted]	3.376	3.233	[redacted]
6) Applying the modified correction factor*	[redacted]	£14,974	£3,061	[redacted]	3.346	3.190	[redacted]
7) Adjusting the population's SMR value	[redacted]	£13,028	£2,414	[redacted]	2.784	2.667	[redacted]
8) Correcting the acquisition costs for glycopyrronium bromide	[redacted]	£13,956	£2,939	[redacted]	3.371	3.233	[redacted]
ERG base case (scenarios 2 – 8)	[redacted]	£10,001	£2,515	[redacted]	4.014	3.992	[redacted]
ERG base case (probabilistic results)	[redacted]	£9,832	£2,321	[redacted]	3.747	3.724	[redacted]
ERG base case (using the NG utility values, i.e. excluding scenarios 1 and 2)	[redacted]	£10,001	£2,515	[redacted]	2.740	2.632	[redacted]
9) Assuming all patients require an ultrasound scan for the CBTA injections†	[redacted]	£10,001	£2,515	[redacted]	4.014	3.992	[redacted]
10) Assuming no additional resource use for the different sialorrhoea severity levels†	[redacted]	£7,759	£0	[redacted]	4.014	3.992	[redacted]

□ This produces more QALYs than the base case due to the continuity correction applied in the mild health state *In conjunction with scenario 5 †In conjunction with the ERG base case

CBTA, Clostridium botulinum toxin A; Glyc Br, Glycopyrronium Bromide; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, Standard of Care

Table 5: Exploratory model results for entire population (with PAS)

Analysis	Discounted costs			Discounted QALYS			ICER (CBTA + SoC versus SoC)
	CBTA + SoC	Glyc Br + SoC	SoC	CBTA + SoC	Glyc Br + SoC	SoC	
Company base case	[redacted]	£14,966	£3,010	[redacted]	3.342	3.202	[redacted]
1) Using the company's LCMM model	[redacted]	£14,966	£3,010	[redacted]	4.917	4.878	[redacted]
2) Applying the ERG's LCMM utility values	[redacted]	£14,966	£3,010	[redacted]	4.879	4.850	[redacted]
3) Correcting CBTA administration costs	[redacted]	£14,966	£3,010	[redacted]	3.342	3.202	[redacted]
4) Severe patients discontinue active treatment after second treatment cycle	[redacted]	£10,972	£3,010	[redacted]	3.296	3.202	[redacted]
5) Mild patients who discontinue active treatment, transition to the moderate health state[]	[redacted]	£14,959	£3,010	[redacted]	3.347	3.202	[redacted]
6) Applying the modified correction factor*	[redacted]	£15,047	£3,142	[redacted]	3.314	3.154	[redacted]
7) Adjusting the population's SMR value	[redacted]	£13,092	£2,485	[redacted]	2.756	2.636	[redacted]
8) Correcting the acquisition costs for glycopyrronium bromide	[redacted]	£14,021	£3,010	[redacted]	3.342	3.202	[redacted]
ERG base case (scenarios 2 – 8)	[redacted]	£9,730	£2,594	[redacted]	4.008	3.987	[redacted]
ERG base case (probabilistic results)	[redacted]	£9,384	£2,396	[redacted]	3.714	3.691	[redacted]
ERG base case (using the NG utility values, i.e. excluding scenarios 1 and 2)	[redacted]	£9,730	£2,594	[redacted]	2.703	2.597	[redacted]
9) Assuming all patients require an ultrasound scan for the CBTA injections†	[redacted]	£9,730	£2,594	[redacted]	4.008	3.987	[redacted]
10) Assuming no additional resource use for the different sialorrhoea severity levels†	[redacted]	£7,405	£0	[redacted]	4.008	3.987	[redacted]

[] This produces more QALYs than the base case due to the continuity correction applied in the mild health state * In conjunction with scenario 5 †In conjunction with the ERG base case

CBTA, Clostridium botulinum toxin A; Glyc Br, Glycopyrronium Bromide; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, Standard of Care

3.3 One-way deterministic sensitivity analysis incorporating the PAS

The ERG's tornado diagrams are presented in Appendix 2 (assuming a cost per QALY gained threshold of £20,000) and Appendix 3 (assuming a cost per QALY gained threshold of £30,000). The deterministic results remain robust. The incremental net monetary benefit (NMB) associated with CBTA + SoC was higher than glycopyrronium bromide arm, whereas it was below zero (indicating an ICER above the threshold) compared with SoC alone.

3.4 Threshold analysis incorporating the PAS

A threshold analysis was undertaken to determine the utility difference between the three different health states needed to be obtain to provide a cost per QALY gained of £20,000 and £30,000.. At an ICER of £20,000 per QALY gained, the differences needed to increase by [redacted] times, [redacted] times, and [redacted] times for severe patients, moderate patients, and the overall population respectively. These factors were [redacted], [redacted] and [redacted] at an ICER of £30,000 for patients with severe, moderate, and combined severity respectively. The disutilities that these multipliers equate to are provided in Table 6 and Table 7.

Table 6: The disutilities required with the sialorrhoea severity states in order to reach a cost per QALY gained value of £20,000

	An initial population with severe sialorrhoea	An initial population with moderate sialorrhoea	An initial population with severe or moderate sialorrhoea
Disutility associated with moderate sialorrhoea[†]	[redacted]	[redacted]	[redacted]
Disutility associated with severe sialorrhoea[†]	[redacted]	[redacted]	[redacted]

[†] Compared with mild / resolved sialorrhoea.

Table 7: The disutilities required with the sialorrhoea severity states in order to reach a cost per QALY gained value of £30,000

	An initial population with severe sialorrhoea	An initial population with moderate sialorrhoea	An initial population with severe or moderate sialorrhoea
Disutility associated with moderate sialorrhoea[†]	[redacted]	[redacted]	[redacted]
Disutility associated with severe sialorrhoea[†]	[redacted]	[redacted]	[redacted]

[†] Compared with mild / resolved sialorrhoea.

Appendix 1: The ERG's probabilistic results. PAS incorporated

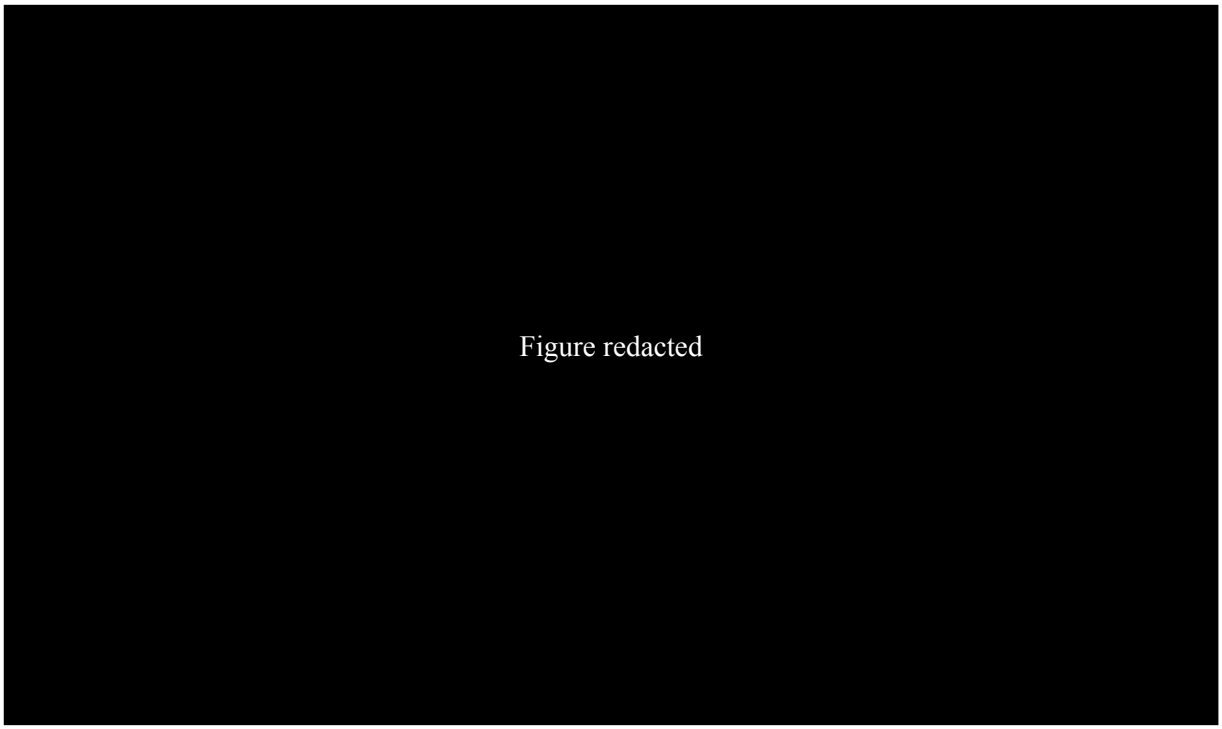

Figure 1: ERG's base case cost–effectiveness acceptability curve (severe patients)

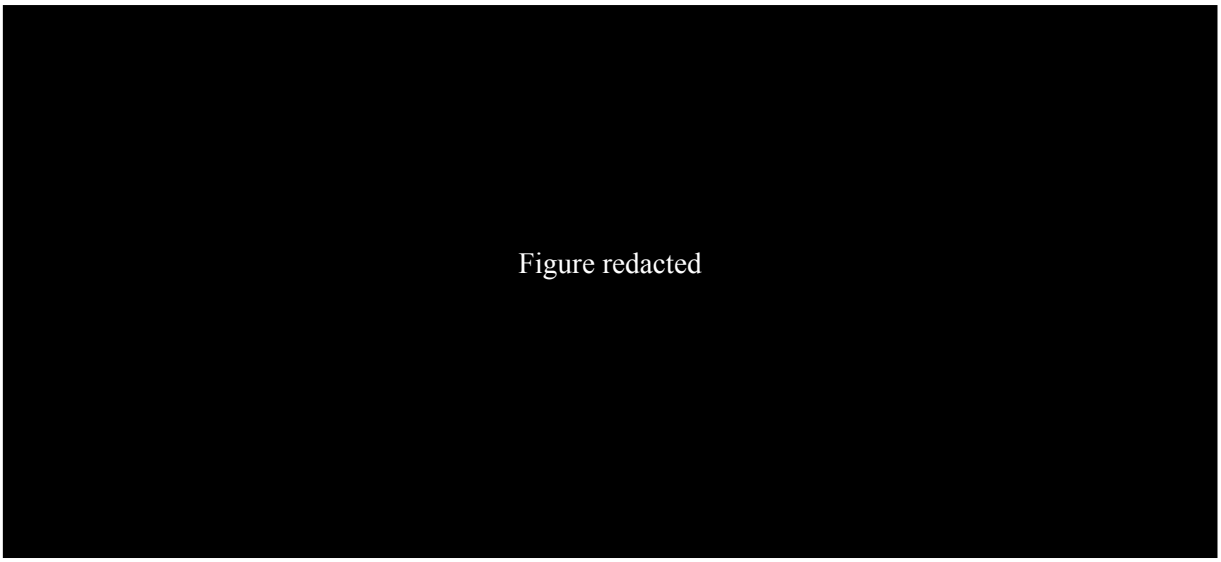

Figure 2: ERG's cost-effectiveness planes of CBTA + SoC (severe patients) versus (i) SoC alone (left side) (ii) glycopyrronium bromide (right side)

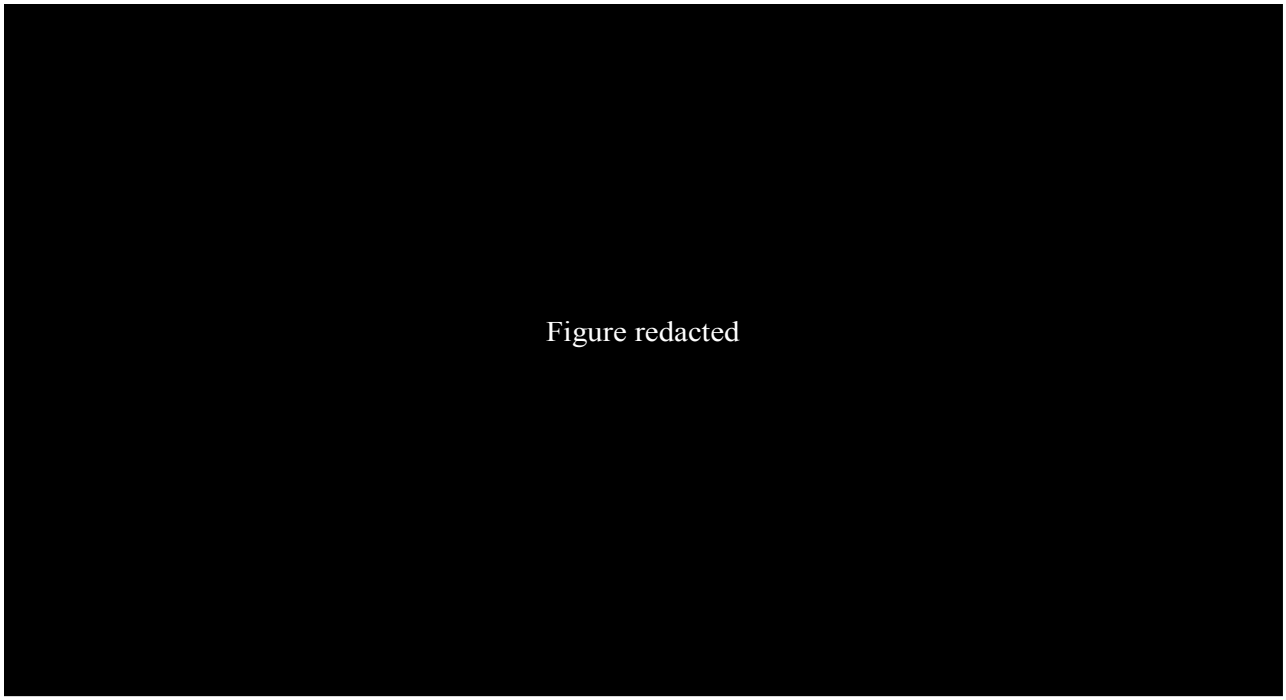

Figure 3: ERG's base case cost–effectiveness acceptability curve (moderate patients)

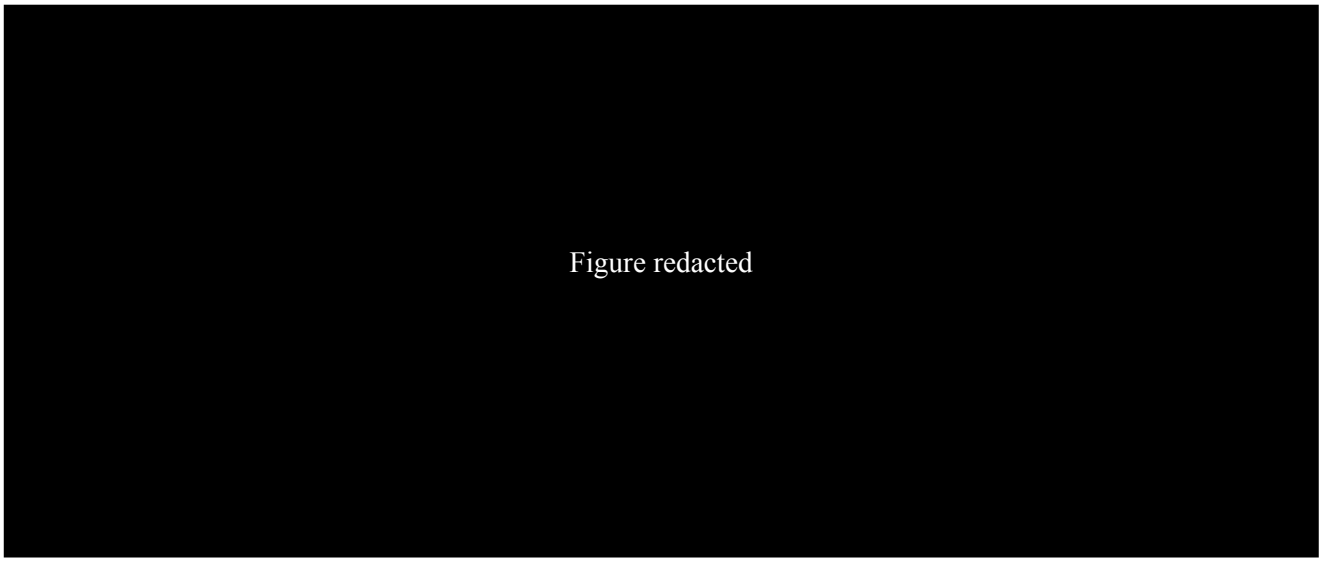

Figure 4: ERG's cost-effectiveness planes of CBTA + SoC (moderate patients) versus (i) SoC alone (left side) (ii) glycopyrronium bromide (right side)

Figure 5: ERG's base case cost–effectiveness acceptability curve (overall population)

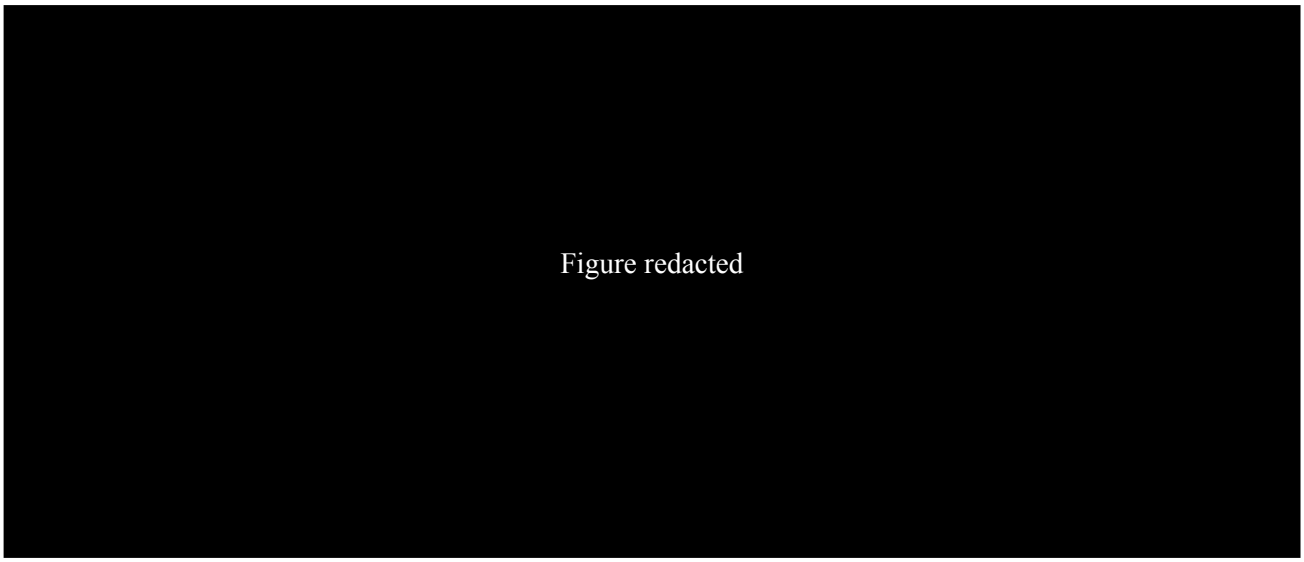

Figure 6: ERG's cost-effectiveness planes of CBTA + SoC (overall population) versus (i) SoC alone (left side) (ii) glycopyrronium bromide (right side)

Appendix 2: ERG's one-way sensitivity analyses (tornado plots) at the £20,000/QALY threshold. PAS incorporated

Figure 7: CBTA plus SoC vs. SoC tornado plot (ERG base case - severe patients)

Figure 8: CBTA plus SoC vs. glycopyrronium bromide tornado plot (ERG base case - severe patients)

Figure 9: CBTA plus SoC vs. SoC tornado plot (ERG base case - moderate patients)

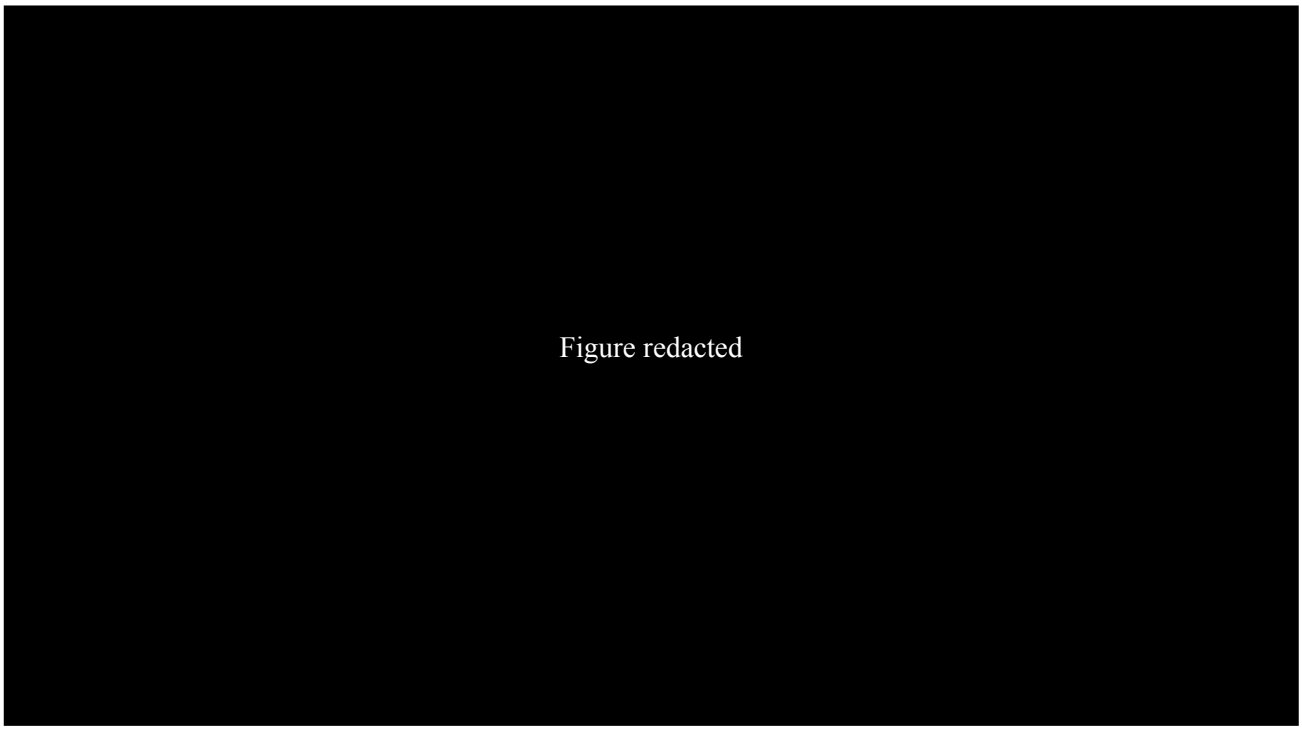

Figure 10: CBTA plus SoC vs. glycopyrronium bromide tornado plot (ERG base case - moderate patients)

Appendix 3: ERG's one-way sensitivity analyses (tornado plots) at the £30,000/QALY threshold. PAS incorporated

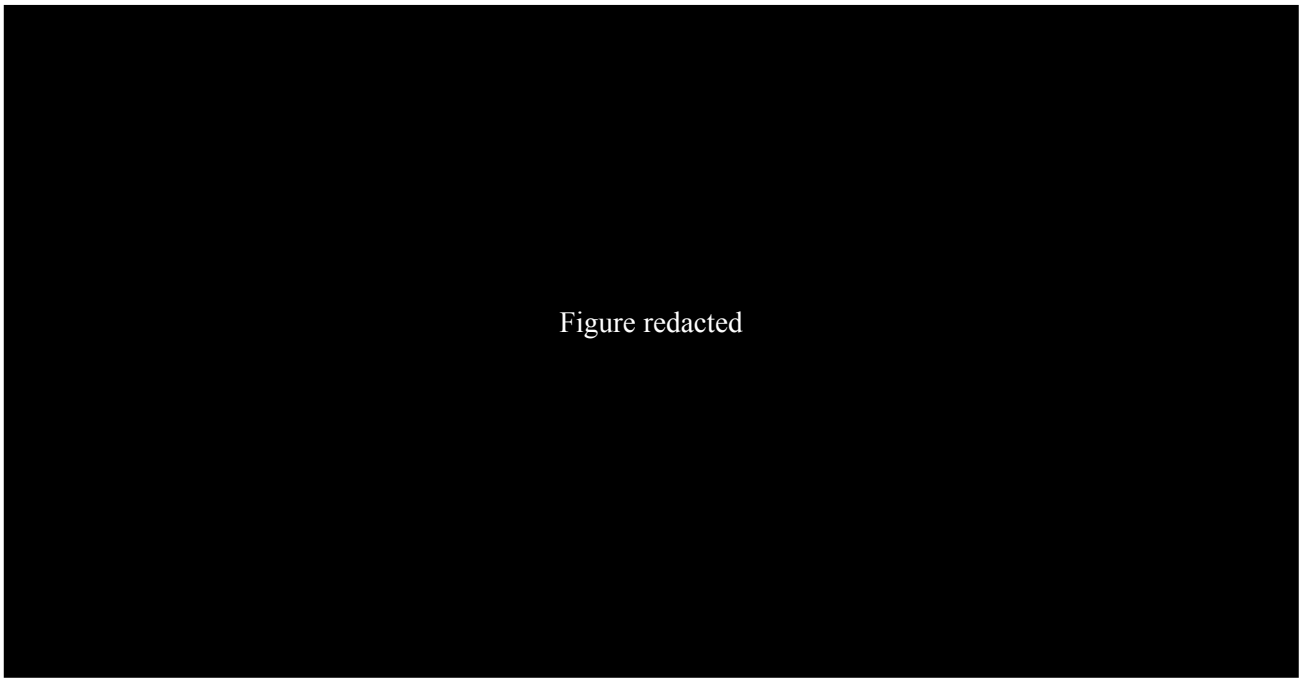

Figure 11: CBTA plus SoC vs. SoC tornado plot (ERG base case - severe patients)

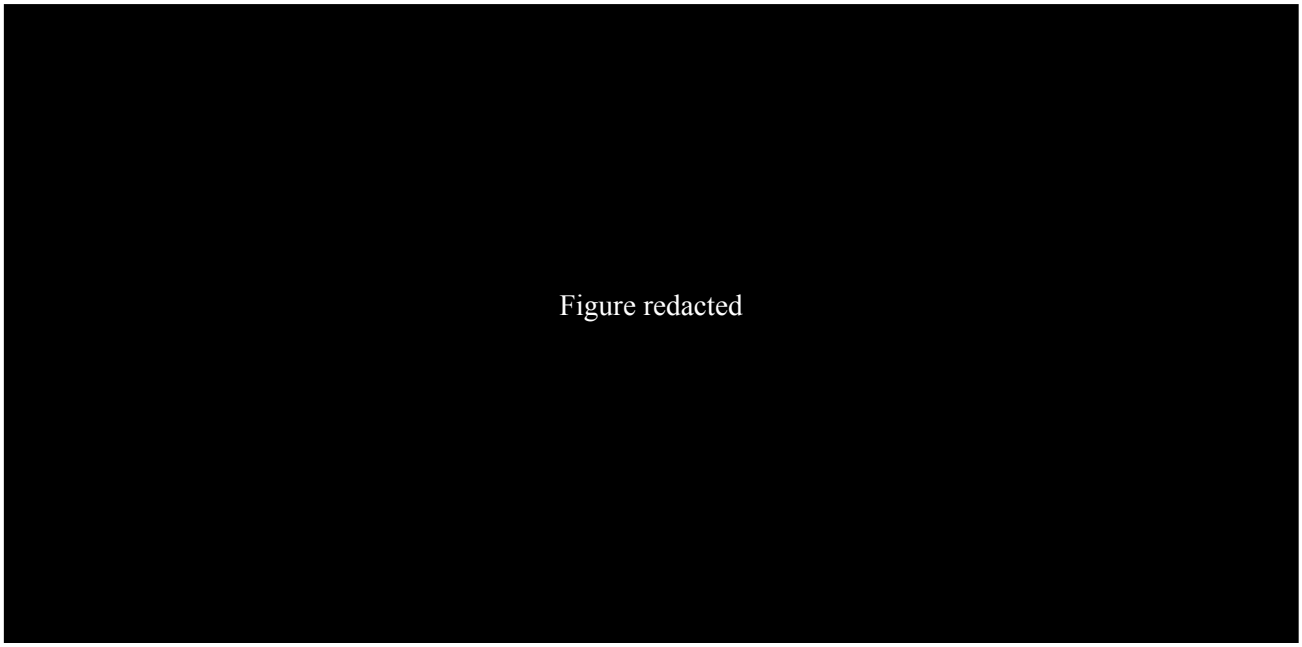

Figure 12: CBTA plus SoC vs. glycopyrronium bromide tornado plot (ERG base case - severe patients)

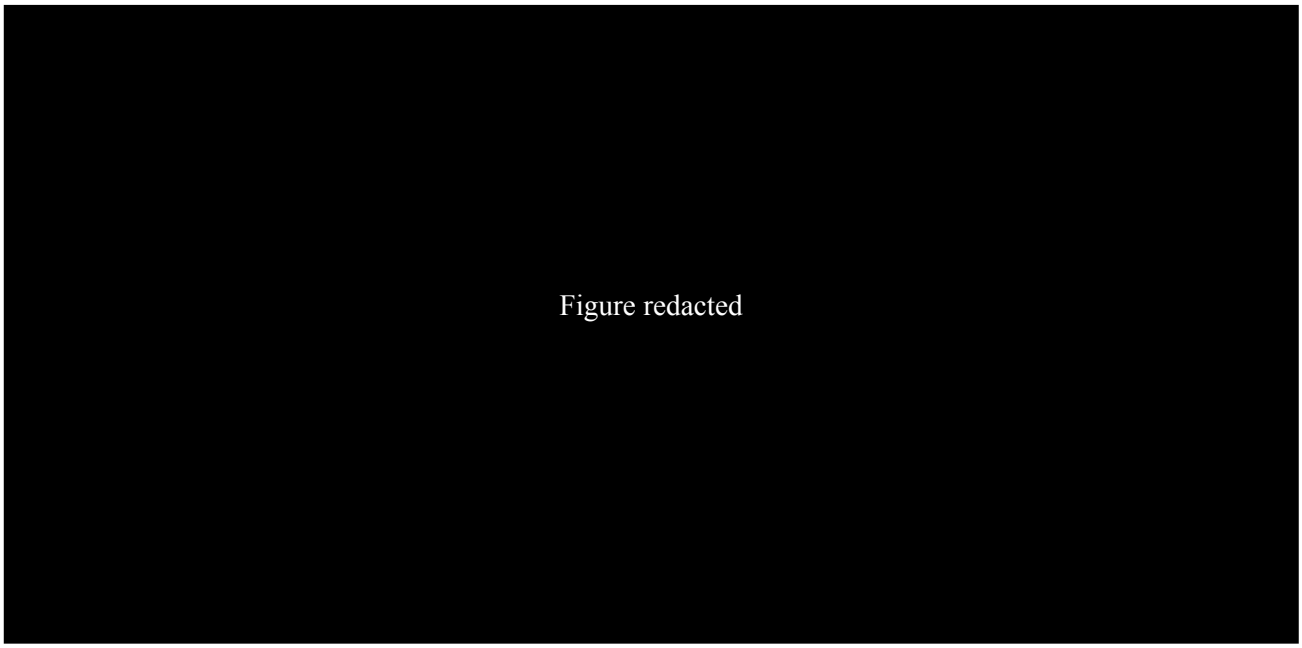

Figure 13: CBTA plus SoC vs. SoC tornado plot (ERG base case - moderate patients)

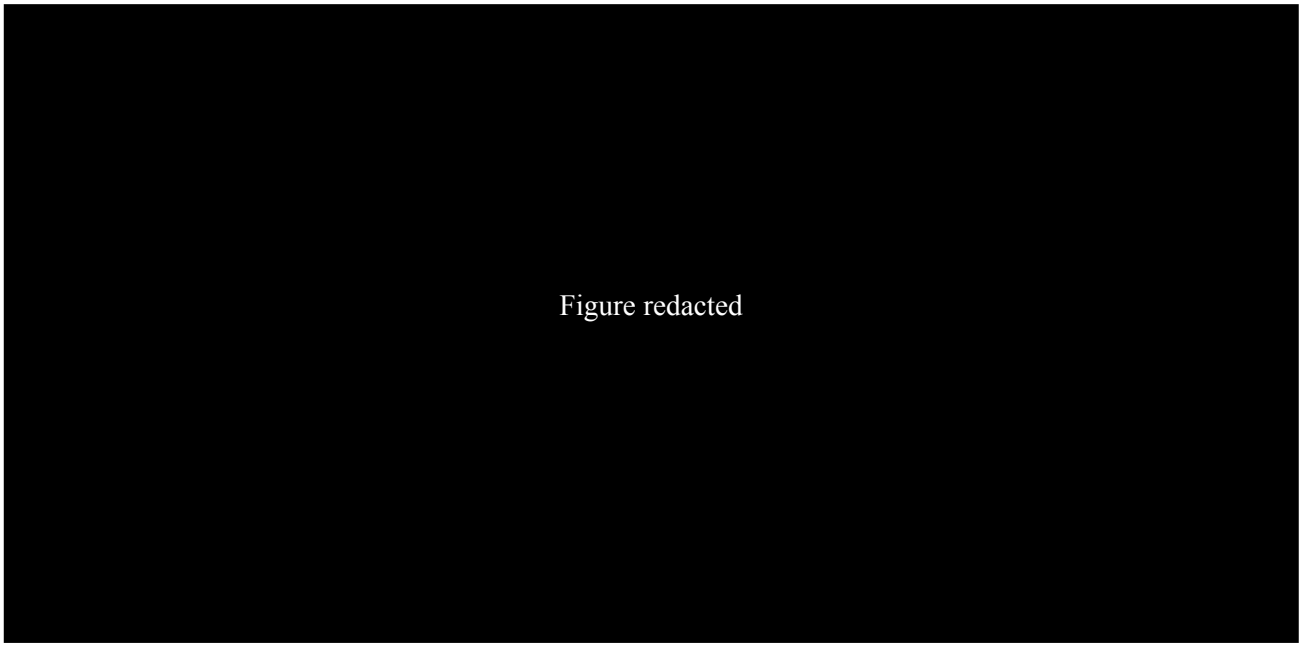

Figure 14: CBTA plus SoC vs. glycopyrronium bromide tornado plot (ERG base case - moderate patients)

1. Merz Pharma UK Ltd. Clostridium botulinum toxin A for treating chronic sialorrhoea [ID1150]. Company's response to clarification questions from the ERG. 2019.
2. Stevenson M, Ren S, Simpson E, Metry A, Orr M, Wong R. Clostridium botulinum neurotoxin type A for treating chronic sialorrhoea: A Systematic Review; 2019.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final technical report

Clostridium botulinum toxin A for treating chronic sialorrhoea

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: July 2019

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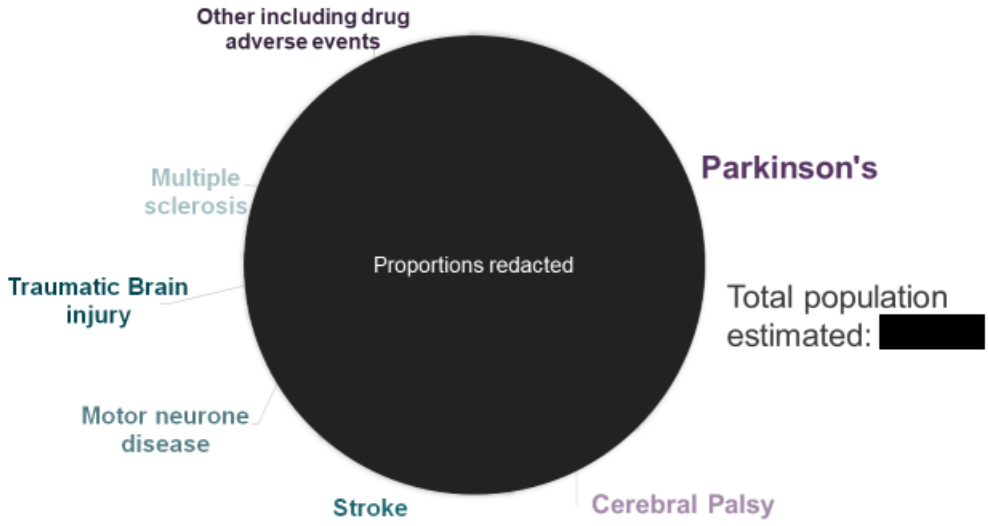
1. Topic background

1.1 Disease background

- Sialorrhoea is the inability to control oral secretions resulting in excessive saliva accumulation
- Inconsistently defined term, could mean:
  - **Drooling –** uncontrollable loss of saliva from the mouth (anterior loss)
  - **Hypersalivation –** excess production of saliva from parotid, submandibular and sublingual glands
- Common symptom of many neurological conditions
- Ineffective swallowing, inadequate rate of swallowing and poor lip seal are considered primary causes of sialorrhoea for many neurological conditions
- Additional burden of sialorrhoea with underlying neurological condition includes:
  - Psychosocial impact
  - Risk of aspiration pneumonia
  - Other consequences from accumulation of saliva

1.2 Prevalence by sialorrhoea aetiology

- Unclear proportions from each patient population, estimates below:



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1.3 Patient perspective

Symptoms

- Psychosocial impact – social embarrassment, decreased self-esteem, social isolation
- Oral hygiene – perioral dermatitis, bad breath, increased bacteria
- Sleep disturbance, dehydration and fatigue
- Risk of aspiration pneumonia if saliva is inhaled (5-10% of patients)
- Caregiver burden of managing drooling

Current experience of treatment

- Variable psychosocial impact dependent on age, severity and condition
- Standard of care involves bibs as well as speech, language and occupational therapy
- Some pharmacological management options available and intervention is already available as a second line treatment

1.4 Information on the technology

Clostridium botulinum toxin A (CBTA) (Xeomin, Merz)

Mechanism	• Blocking surrounding nerves that control saliva production in the parotid and submandibular salivary glands
Marketing authorisation	• CHMP positive opinion May 2019: "treatment of adults with chronic sialorrhoea due to neurological conditions"
Administration and dose	• 100 units per administration injected into the parotid and submandibular glands
List price	• £129.90 per 100 unit vial (£422.18 annual cost) • Confidential PAS discount available

Other indications	• Xeomin is indicated for blepharospasm, cervical dystonia of a predominantly rotational form (spasmodic torticollis) and spasticity of the upper limb in adults
	• Other CBTA and CBTB products are indicated for:
	  • Focal spasticity
	  • Chronic migraine
	  • Bladder disorders
	  • Skin and skin appendage disorders

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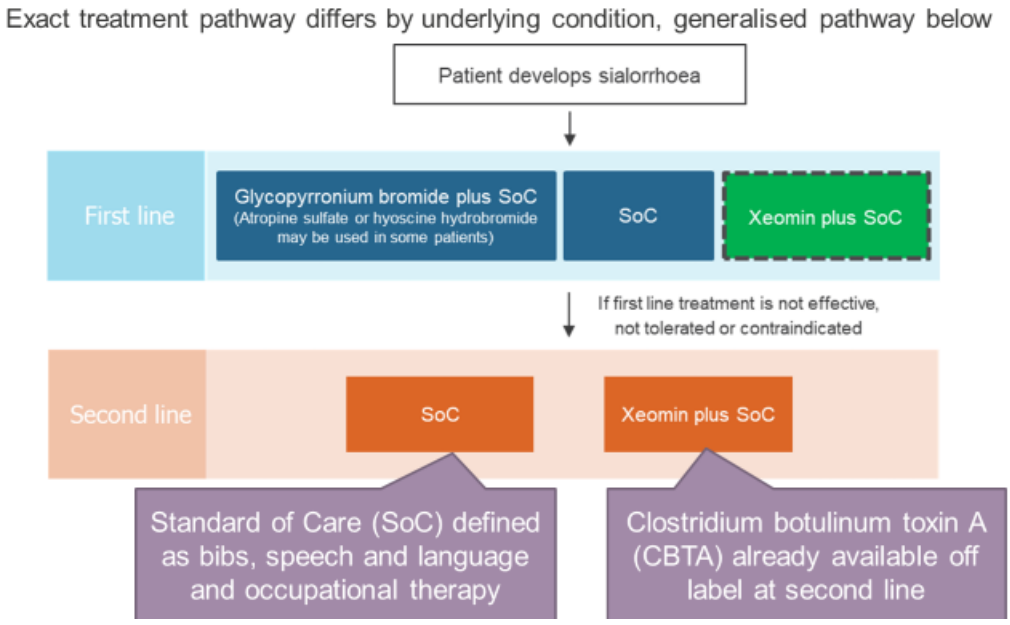
1.5 Treatment pathway



1.6 Professional group comments

Aims of treatment
- Reduce excess saliva production, which results in unpleasant dribbling onto clothes and irritation at the corners of the mouth

Current treatment options
- Limited – anticholinergic therapy can cause cognitive and neuropsychiatric problems, particularly when there is cognitive impairment

Clinical need
- Need for a targeted treatment that avoids systemic side effects
- Not required in most patients

Informal stopping rules
- Lack of benefit assessed by adjusting doses and sites over 3 consecutive treatment cycles and deciding if benefit is evident – stopping if not
- Some patients become immune to CBTA and there is an option to try CBTB
- Also stopped if significant side effects develop

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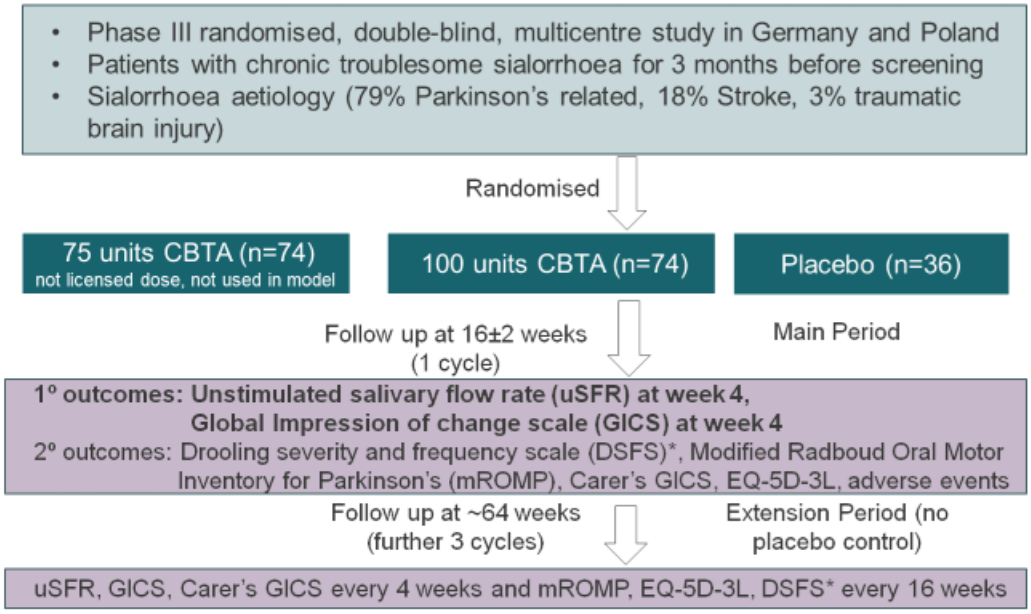
1.7 Decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission
Population	Adults with chronic sialorrhoea	As per final scope
Intervention	CBTA with standard care	As per final scope
Comparator	• Anticholinergic drugs such as glycopyrronium bromide For people in whom anticholinergic drugs are unsuitable: • Established clinical management	• Glycopyrronium bromide For people in whom anticholinergic drugs are unsuitable: • Standard of care (SoC; basic non-pharmacological management
Outcomes	The outcome measures to be considered include: - Unstimulated salivary flow rate - Response rates - Adverse effects of treatment - Health-related quality of life	Additional including: • Global impression of change scale (GICS) • Drooling severity and frequency score (DSFS)

1.8 SIAXI study design



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1.9 Outcome measures

Co-primary outcomes

Unstimulated salivary flow rate (uSFR)

Calculated by swab method – weight of 4 absorbent rolls placed at the orifices of the salivary glands over 5 minute period (g/min)

Unclear if there is association with health-related quality of life

Global Impression of Change (GICS)

7 point Likert scale from -3 (much worse) to +3 (much improved) asked about function compared with time of last injection.

Outcome used in economic model

Drooling Severity and Frequency Scale (DSFS)

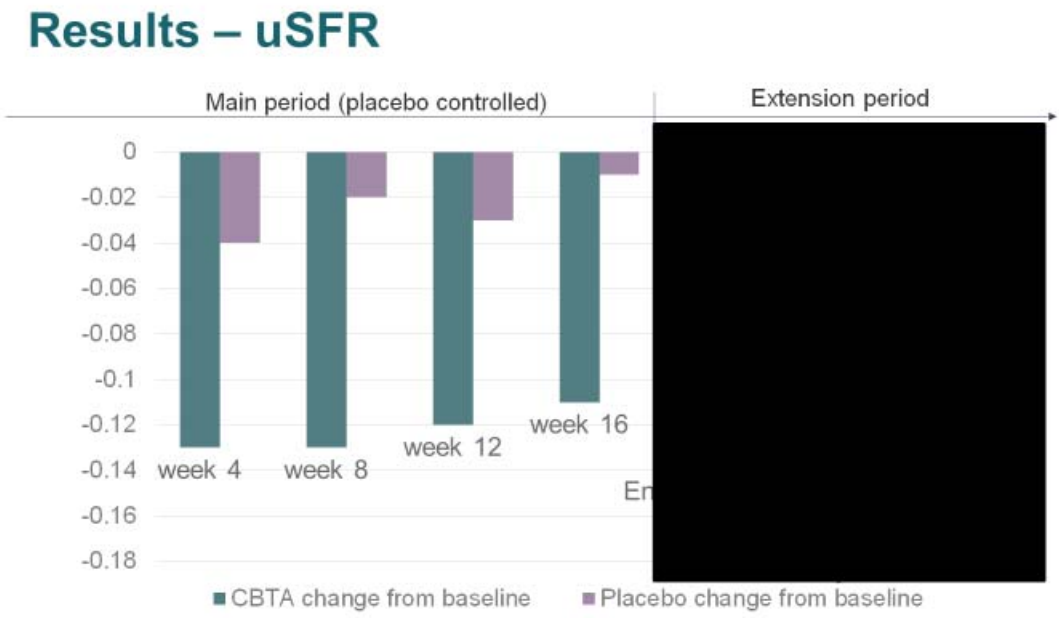
Two subscales added together:

- A 4-point Likert scale for drooling frequency 1 (never) to 4 (constantly)
- A 5-point Likert scale for drooling severity 1 (dry) to 5 (profuse)

Not validated with health-related quality of life and unclear if there is association

Transitions between DSFS states modelled in the economic analysis

1.10 Results



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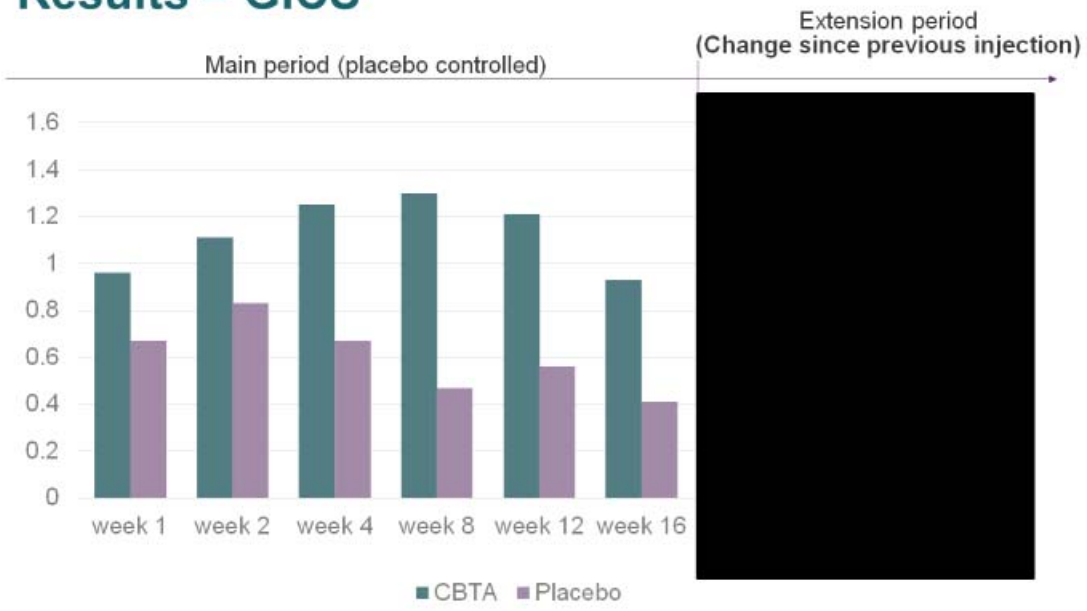
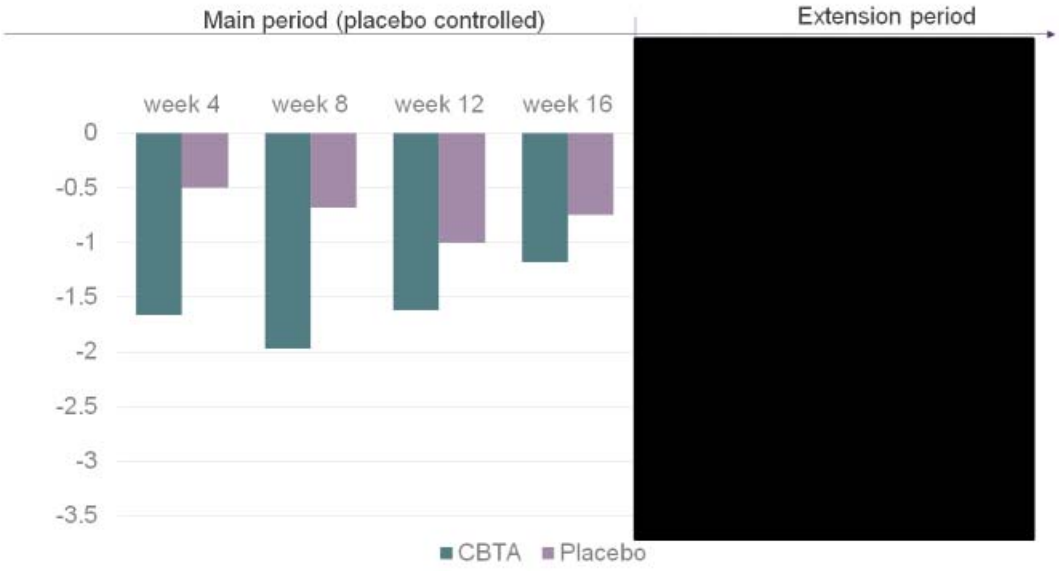
Results – GICS



Results - DSFS



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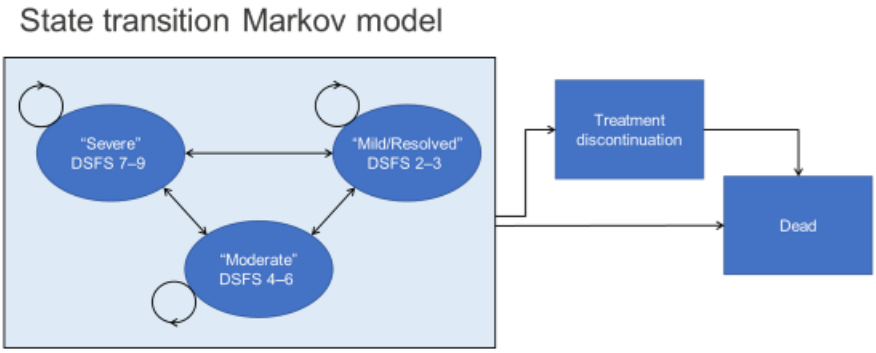
1.11 Economic model structure



- 3 health states defined by DSFS score
- Baseline DSFS score from SIAXI baseline
- Patients can transition between any state
- Patients that discontinue revert to mean baseline
- Any state can independently transition to death

- Time horizon: 10 years
- 3.5% discount rate
- NHS/PSS perspective
- 16-week cycle length

1.12 Key model assumptions

Comparators	• CBTA with standard of care compared with:
	  • glycopyrronium bromide with standard of care
	  • standard of care alone
	• Costs of atropine sulfate and hyoscine hydrobromide considered in scenario analysis

Source of QALY gain	• No excess mortality modelled in company base case, all QALY gains are from increased health-related quality of life • Alternative standardised mortality rates explored in scenario analysis
Adverse events	• No adverse events modelled due to lack of data
Utilities	• Company base case uses estimated utility values from NG62 guideline stratified into 3 health states based on DSFS • Company considers EQ-5D to be insensitive to sialorrhoea-related changes in quality of life in the SIAXI population
Costs and resource use	• All drug costs at list prices on BNF • Administration costs based on NHS outpatient reference cost and ultrasound scan for the same % as received a scan in SIAXI • Other health-state costs based on NHS speech pathology and occupational therapy consultation costs

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2. Summary of the draft technical report

2.1 After technical engagement the technical team has collated the comments received and, if relevant, updated the scientific judgement by the technical team and rationale. Scientific judgments that have been updated after engagement are highlighted in **bold** below.

2.2 In summary, the technical team considered the following:

Issue 1 **The most appropriate comparator over a lifetime horizon is standard of care although glycopyrronium bromide may be used in the short term for some patients**.

Issue 2 **Health-related quality of life as measured by the EQ-5D is the most appropriate outcome of the trial although DSFS is the most relevant clinical outcome and may correlate with health-related quality of life**.

Issue 3 **The EQ-5D-3L questionnaire used in SIAXI trial is the most appropriate measure of health-related quality of life and the most appropriate source of utility values but there is uncertainty around the sensitivity of the questionnaire.**

Issue 4 **There is variability across UK practice on the use of ultrasound imaging for administering injections, therefore it is appropriate that the proportion of people that received ultrasound injections in the trial are accounted for in the model.**

Issue 5 **The resource costs in the model do not take account of additional training and resources that may be required.**

2.3 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The marketing authorisation for the comparator glycopyrronium bromide (an anticholinergic) is for children and adolescents with severe sialorrhoea, although it is used in clinical practice outside its marketing

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authorisation for people with Parkinson's disease and motor neurone disease. Therefore, there is limited evidence on the clinical effectiveness of glycopyrronium bromide. In the company submission, it is assumed to be 75% as effective as clostridium botulinum toxin A (CBTA) based on analysis in NG62 guideline for cerebral palsy in under 25s.

- Other anticholinergic treatments (such as atropine sulphate or hyoscine hydrobromide) do not have marketing authorisations in the UK and so are used in clinical practice outside their marketing authorisations. Therefore, there is limited evidence on the clinical effectiveness of other anticholinergic treatments. In the company submission, it is assumed these are equivalent to glycopyrronium bromide.
- The costs and disutilities associated with adverse events of CBTA and glycopyrronium bromide are not included in the model. This is because there is limited safety data on glycopyrronium bromide, and the risks associated with the procedure for CBTA.

2.4 Taking these aspects into account, the technical team's preferred assumptions result in cost-effectiveness estimates of:

- CBTA dominates glycopyrronium bromide (and other anticholinergic treatments)
- an incremental cost-effectiveness ratio (ICER) of £52k per QALY gained (see table 1) against standard of care.

2.5 The technology is unlikely to be considered innovative.

2.6 No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

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3. Key issues for consideration

Issue 1a – Comparators

Questions for engagement	1. What active treatments are used to treat sialorrhoea in NHS clinical practice? Does it vary by the underlying aetiology? 2. Is the company's positioning of CBTA appropriate for all neurological conditions associated with sialorrhoea?
Background/description of issue	**The company** has positioned CBTA as a first- and second-line treatment. The company has positioned CBTA as an active treatment alongside non-pharmacological management (including bibs, as well as speech, language and occupational therapy [standard of care]) and pharmacological treatments. Second-line, the company has positioned CBTA alongside non-pharmacological treatments. **See section 1.4: The company's anticipated positioning of CBTA within the current clinical pathway** Active pharmacological management of sialorrhoea can include several anticholinergic treatments such as glycopyrronium bromide, hyoscine hydrobromide and atropine sulphate and other antispasmodic treatments such as trihexyphenidyl. None of these treatments have marketing authorisations for the entire population of sialorrhoea and the treatments differ depending on the underlying neurological condition associated with sialorrhoea. Active non-pharmacological management may also include radiotherapy or surgery on the salivary glands.

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	The guideline for motor neurone disease (NG42) recommends an anticholinergic treatment as a first-line treatment, specifying glycopyrronium bromide as the choice for people with cognitive impairment because it has fewer central nervous system side effects. If this treatment is not effective, not tolerated or contraindicated, the guideline recommends referral for CBTA treatment. The guideline for Parkinson's disease (NG71) recommends standard of care as a first-line treatment, if this is not effective, then glycopyrronium bromide is recommended. The guideline recommends referral for CBTA treatment as second-line treatment only after glycopyrronium bromide is not effective, not tolerated or contraindicated. The cerebral palsy in under 25's (NG62) guideline recommends hyoscine hydrobromide as first-line treatment, with glycopyrronium bromide or other anticholinergics as second-line treatment only if this is not effective, not tolerated or contraindicated. The guideline recommends referral for CBTA treatment as a third-line treatment only after both treatments are considered not effective, not tolerated or contraindicated. **The company** considered standard of care and glycopyrronium bromide (as the main active treatment comparator) in its clinical and cost effectiveness analyses. The company also considered 2 other anticholinergics in cost effectiveness scenario analyses.
Why this issue is important	It is important to identify the appropriate position for CBTA in the pathway so that all the appropriate comparators for CBTA by treatment population are identified for the appraisal.
Technical team preliminary judgement and rationale	**The technical team** consider glycopyrronium bromide to be the most relevant pharmacological comparator if CBTA is to be used as a first-line treatment option as it is recommended in the NICE clinical guidelines. However, glycopyrronium bromide is only licensed for use for severe sialorrhoea in children with neurological disorders for a short amount of time. Standard of care is also an appropriate comparator if CBTA is to be used as first-line or second-line treatment option (again recommended in the NICE clinical guidelines), However it is unclear which factors affect the decision on whether active treatment is preferred over standard of care (see Issue 1b).

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Summary of comments	Comments from company • Current clinical practice aligns with NICE clinical guidelines • Active treatment options do not vary significantly by aetiology but may depend on underlying co-morbidities, the adverse event profile of the therapies available and patient/clinician choice • The mechanism of action means CBTA avoids polypharmacy which is prevalent in patients with neurological disorders, and avoids adverse events associated with systemic treatments • CBTA is positioned as a first-line active treatment when non-pharmacological management is inadequate Comments from Association of British Neurologists • Oral anticholinergics are frequently used but are not licensed for sialorrhoea Comments from ERG • For the Parkinson's disease guideline (NG71), the positioning of CBTA was driven by the fact that no CBTA products were licensed at the time the guidelines were written. • If a CBTA product was licensed, it would have been the recommended first-line active treatment because of the adverse events associated with glycopyrronium bromide.

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Technical team judgement after engagement	Treatment with CBTA is likely to displace anticholinergic use as a first-line treatment for severe sialorrhoea. However, it will likely displace non-pharmacological management for a considerable amount of people who would be unable to take anticholinergics. Generally, anticholinergics are not well tolerated and cannot be used for extended periods of time. Glycopyrronium bromide is the most used anticholinergic treatment because it does not cross the blood-brain barrier and therefore does not have the cognitive side-effects of other anticholinergics. However, the summary of product characteristics states that treatment would be repeated intermittently in the non-palliative setting which will be equivalent to standard of care during off-treatment. For these reasons, the technical team consider standard of care as the most appropriate comparator in the first-line severe chronic sialorrhoea setting over a lifetime horizon but consideration will be given to glycopyrronium bromide as a comparator to CBTA as a first-line treatment option for severe sialorrhoea in the short term.

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Issue 1b – Treatment choice

Questions for engagement	3. What factors affect the decision on whether active treatment is preferred over standard of care? In particular: • Does the decision change based on underlying neurological condition that causes sialorrhoea? • Does the decision change based on severity of sialorrhoea? Is severe sialorrhoea a distinct subgroup from moderate sialorrhoea? 4. What factors affect the decision to discontinue active treatment? In particular: • Will any rules be used to assess whether CBTA is stopped? • If CBTA was available as a first-line treatment, how would this affect the pathway? Would anticholinergics still be considered first? Is development of an immunity to CBTA a consideration of treatment?
Background/description of issue	Sialorrhoea can affect people with different underlying neurological conditions, it is unclear how patient and clinician choice of treatment affects the pathway for each condition. It is also unclear whether severity of sialorrhoea is an important factor in the patient and clinician choice of treatment. Glycopyrronium bromide is only licensed for use over short periods of time due to the potential for adverse effects, this may also be true for other active treatments. People who choose to receive standard of care at first line may not choose to try any active treatment at second line. Therefore, it is unclear what causes discontinuation of active treatments (including when CBTA would be discontinued). Reasons for discontinuation may include the possibility of developing immunity to CBTA and the potential for using clostridium botulinum toxin B as an alternative.
Why this issue is important	It is unclear which patient populations would choose to take active treatments including CBTA in clinical practice and which would choose no active treatment. It is important to identify the factors that affect patient and clinician treatment choice (e.g. licensing status, side effect profile), including reasons for discontinuation of treatment, and how this affects the clinical treatment pathway.

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Technical team preliminary judgement and rationale	It is possible that people with sialorrhoea will have different attitudes towards the condition and different preferences for treatment. The large proportion of patients that choose standard of care over active treatment suggests people may weigh the benefits of treatment against adverse events. It is unclear if patients would consider the risk of CBTA procedure to outweigh its benefits. As a result of this variability in reasoning behind treatment choice, the treatment pathway is uncertain. However, in a setting where patient and clinician preferences are critical, it seems inappropriate to limit CBTA as a treatment option by underlying neurological condition or severity.

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Summary of comments	Comments from company • The decision about whether to use an active treatment would not differ based on the underlying cause of a specific neurological disorder. • It would also depend on severity, co-morbidities and patient/ clinician choice. • For moderate to severe sialorrhoea, non-pharmacological management is unlikely to be sufficient. • Severe sialorrhoea is not a distinct subgroup, clinicians may use different measure to determine severity of sialorrhoea. • CBTA would be stopped due to lack of efficacy, contraindications, adverse events or patient/clinician preference. • There are no formal stopping rules, however some clinicians may choose to stop treatment after 2 injection cycles if there was no benefit. • There is no evidence to suggest development of immunity to CBTA would lead to loss of response, this has been demonstrated in over 2 million treatment episodes, and 12 years of post-marketing surveillance. Comments from Association of British Neurologists • The decision about whether to use an active treatment is based on subjective and objective severity of sialorrhoea, efficacy of previous treatment and other individual patient suitability considerations. • Severe sialorrhoea is not a distinct subgroup and severity of sialorrhoea can fluctuate • CBTA would be stopped if there was a lack of efficacy or side effects, particularly involving impaired swallowing. • Anticholinergics are not ideal for many patients due to adverse cognitive effects and have poor long-term tolerability, so CBTA would be preferable. Comments from ERG

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	Despite NICE recommendations to consider anticholinergics, lack of evidence and adverse events limit their use.
Technical team judgement after engagement	The decision about patient and clinician choice of active treatment does not depend on underlying neurological condition. Severity of sialorrhoea is assessed by physical examination and detailed patient history, the degree of severity can fluctuate and therefore severe sialorrhoea is not a distinct subgroup. Therefore, it is inappropriate to limit treatment options based on either underlying neurological condition or severity. There are no formal stopping rules for CBTA. Response to CBTA would be judged on a subjective assessment of reduction in drooling or the presence of adverse events such as facial muscle weakness, palsy and impaired swallowing. Assessment would informally take place after two injection cycles (32 weeks) but the technical team note that the cost-effectiveness results are not sensitive to the application of a stopping rule. It is unlikely that Xeomin would be discontinued as a result of the development of immunity to CBTA, therefore concerns about immunity have been resolved.

Issue 2 – Outcomes

Questions for engagement	5. What outcome measures are appropriate for measuring sialorrhoea?
Background/description of issue	Sialorrhoea is an inconsistently defined term which could refer to drooling (loss of saliva from the mouth) or hypersalivation (overproduction of saliva from the salivary glands). People may have a subjective response to treatment depending on what outcomes are important to them and the mechanism of their sialorrhoea. There are no standardised diagnostic or severity assessment tools for sialorrhoea. The SIAXI trial co-primary outcome measures were unstimulated salivary flow rate (uSFR) (measured by weight of saliva production) and global impression of change (GICS) which was a 7-point Likert scale of change, both measured at 4 weeks. Additional outcomes included the drooling severity and frequency scale (DSFS), Modified Radboud Oral Motor

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	Inventory for Parkinson's disease (mROMP) and Carer's GICS, measured throughout the trial. It is unclear what the most appropriate measurement of sialorrhoea is (and therefore response to treatment). uSFR measures saliva production which may not correlate with outcomes important to people with sialorrhoea, because most underlying neurological problems affect saliva clearance and there are side effects including thicker saliva and dry mouth. It is also unclear when these measurements should be taken to appropriately evaluate response to treatment.
Why this issue is important	The key driver of cost effectiveness is health-related quality of life as CBTA does not have an effect on survival. The appraisal therefore needs to determine whether CBTA increases the QALY gain by increasing health related quality of life. It is important to understand the clinical benefit as measured by the outcome choice, and the effect of that clinical benefit on health-related quality of life.
Technical team preliminary judgement and rationale	**The technical team** consider that it may be most appropriate to directly measure the health-related quality of life benefit from EQ-5D-3L measurements (see section 3a).
Summary of comments	Comments from company • The outcome measures used to assess severity of sialorrhoea may vary in clinical practice, depending on the underlying aetiology. • Control of salivation severity and frequency is a key goal in the treatment of sialorrhoea, therefore the outcomes measured in the trial are relevant to patients and clinicians • DSFS is considered to be the most clinically relevant measure of disease severity, it is a subjective scale which correlated well with the disease burden associated with sialorrhoea. Comments from Association of British Neurologists • Scoring systems are not part of standard clinical practice, sialorrhoea is measured by physical examination and a detailed history from the patient and carers.

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Technical team judgement after engagement	None of the outcomes for measuring sialorrhoea in the SIAXI trial are used in standard clinical practice. However, DSFS can be considered the most relevant clinical outcome measure for disease severity because it most likely to correlate with the disease burden of sialorrhoea. Although drooling severity and frequency are most likely to correlate with health-related quality of life, it is unclear how a change in DSFS score would correlate with a change in EQ-5D-3L. After engagement, the technical team still consider that it is most appropriate to directly measure the impact of drooling on health-related quality of life with EQ-5D-3L. However, Issue 3a describes the potential problems with the EQ-5D-3L measurement of health-related quality of life for patients with sialorrhoea.

Issue 3a – Health-related quality of life (EQ-5D-3L)

Questions for engagement	6. Which symptoms associated with sialorrhoea have the highest impact on quality of life? 7. Is the EQ-5D-3L questionnaire used in the SIAXI trial sensitive to health-related quality of life changes associated with freedom from sialorrhoea? 8. Are the EQ-5D-3L results from the SIAXI trial generalisable to the entire population of people with sialorrhoea?
Background/description of issue	The symptoms associated with sialorrhoea include poor oral hygiene, bad breath, eating and speaking difficulty, sleep disturbance, dehydration and the risk of aspiration pneumonia. There is limited evidence on the effect of these symptoms on health-related quality of life and it may differ depending on the underlying neurological condition. The SIAXI trial measured quality of life using the EQ-5D-3L questionnaire, however it showed no statistically significant change in quality of life after treatment with CBTA. The company suggests this may be because the population of SIAXI has underlying neurological conditions. This means that the value of any improvements in sialorrhoea may

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	be obscured by the health-related quality of life impact of the underlying condition. The majority of patients enrolled within the SIAXI trial responded with a score of 2 (some problems) for all 5 domains at baseline. For an improvement in health-related quality of life because of reduced drooling to register on the EQ-5D-3L, such patients would need to feel able to grade these domains with a score of 1 (no problems) The ERG disagrees and notes that there was a non-significant increase in EQ-5D-3L, and they consider this to represent the impact of CBTA. **The company** did not use the EQ-5D-3L data from the SIAXI trial and instead used utility value data from the guideline cerebral palsy in under 25's (NG62). **The ERG** considers the EQ-5D-3L data from SIAXI to be the most appropriate data to use in the model. This is because it better reflects the entire population of people with sialorrhoea seen in clinical practice. The population in the SIAXI trial consisted of 71% of people with Parkinson's disease and 10% with stroke. Issue 1 describes the wide range of possible underlying neurological conditions of sialorrhoea which may affect the generalisability of these results. The EQ-5D questionnaire also includes a visual analogue scale (EQ-VAS) which measures self-rated health status and therefore gives an approximate measure of subjective response to treatment. [redacted]
Why this issue is important	The health related quality of life data affect the choice of utility values in the economic model (Issue 3b).
Technical team preliminary judgement and rationale	**The technical team** prefer the EQ-5D-3L data from the SIAXI trial because this is consistent with the NICE reference case in the NICE methods guide (section 5.3.10). In addition, the company have not provided qualitative empirical evidence on the lack of content validity for the EQ-5D. However, the technical team acknowledge the possibility that

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	the EQ-5D may not be sensitive to changes in health-related quality of life in the entire population of people with chronic sialorrhoea.
Summary of comments	Comments from company • There is an absence of data on which symptoms have the highest impact on health-related quality of life. • Posterior loss of control of saliva is associated with morbidity and mortality due to aspiration pneumonia which has serious impact on health-related quality of life and cost implications for the NHS – the technical team note that this was not modelled in the company submission. • The adverse event profile of anticholinergics exacerbates common issues for people with neurological conditions • Chronic sialorrhoea may also increase the burden on carers. • The EQ-5D is insensitive to changes in disease severity in disorders that are painful or life-threatening – a previous study in another neurological indication showed that the EQ-5D is insensitive for dysphagia. • Measurement of the impact on quality of life associated with sialorrhoea is difficult in the context of debilitating underlying neurological conditions which may have their own dynamic impact on quality of life. • The EQ-5D-3L measurement only registers change in patient utility where there is a step change in a single domain, however, the majority of patients in the SIAXI trial responded with a score of 2 (some problems) for all 5 domains – in order to register a change the patient would have to grade one of the domains with a score of 1 (no problems). Comments from Association of British Neurologists • The symptoms with the highest impact on quality of life are embarrassment, skin irritation and hygiene issues.

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	• It is unlikely that any of the specific consequences of sialorrhoea would be reliably detected in a non-saliva specific questionnaire. Comments from ERG • The use of utility data from NG62 should not take primacy over the EQ-5D data from the SIAXI trial because disutility was set to an arbitrary value per unit increase in DSFS in a strikingly different population. • The ERG is not convinced by qualitative empirical evidence on the lack of content validity of the EQ-5D, although some arguments about the insensitivity may be plausible. • The EQ-5D-3L may accurately be picking up a small utility gain associated with improved sialorrhoea symptoms. • The small gain in mean utility across sialorrhoea severity states are coherent with the observed patient GICS score.
Technical team judgement after engagement	The symptoms of sialorrhoea with the highest impact on quality of life are consistent with drooling, for example skin irritation, hygiene and psychosocial impact of drooling. The technical team acknowledge that is unlikely that any other specific consequences of drooling would be reliably detected by a non-sialorrhoea specific questionnaire. The technical team also acknowledge that the company have provided a reference to a study in another neurological indication that shows EQ-5D-3L is insensitive for dysphagia. Based on the limited information available on this source, the technical team still prefer the EQ-5D data from the SIAXI trial but note that this will introduce significant uncertainty to the utility values used in economic modelling (see Issue 3b). This uncertainty applies to the severity of the condition as well as a response to treatment.

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Issue 3b – Utility values

<table>
<tr><td>Questions for engagement</td><td>9. What are the most appropriate utility values for people with sialorrhoea?
10. Which of the company or ERG models uses the most plausible utility values?
11. What is the expected utility value gain associated with freedom from severe sialorrhoea?</td></tr>
<tr><td>Background/description of issue</td><td>Because of the issues with health-related quality of life in Issue 2a, the company did not use EQ-5D data from the SIAXI trial to obtain utility values. Instead, the company used utility values stratified by DSFS severity from the NG62 guideline for cerebral palsy in under 25s.
The ERG had concerns that the population from the NG62 guideline was significantly different from the SIAXI population, so the ERG preferred to use a utility regression model using the EQ-5D-3L data from the SIAXI trial.
The results from each model are shown below:
This
<table><tr><th></th><th>ERG model (SIAXI EQ-5D-3L data)</th><th>Company model (NG62-derived values)</th></tr><tr><td>Resolved / Mild (DSFS 2-3)</td><td>0.6397</td><td>0.5346</td></tr><tr><td>Moderate (DSFS 4-6)</td><td>0.5974</td><td>0.4283</td></tr><tr><td>Severe (DSFS 7-9)</td><td>0.5854</td><td>0.3008</td></tr></table>corresponds to a utility value gain of 0.23 associated with freedom from severe sialorrhoea in the company model compared with 0.05 in the ERG model.</td></tr>
<tr><td>Why this issue is important</td><td>The choice of utility values has a large impact on the ICER. Using the ERG model increases the ICER by approximately £38k from the company's model (see table 1).</td></tr>
</table>

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Technical team preliminary judgement and rationale	Because of the judgement expressed in Issue 3a, **the technical team** prefers the ERG modelled utility values. However, the technical team acknowledge the uncertainty around which utility values best represent the entire population of people with sialorrhoea.
Summary of comments	Comments from company • There are very limited utility data for drooling health states and the utility gain associated with freedom from sialorrhoea. • Both sets of utility values are associated with substantial uncertainty. • The "true" utility values likely lie somewhere between the two utility sets, but the NG62 guideline approach is more clinically plausible. • Dysphagia is associated with a disutility of 0.048 in a previous NICE appraisal, this does not capture psychosocial impacts or sleep disturbance of sialorrhoea but shows the extent to which only a part of the impact of sialorrhoea have on utility in other contexts. Comments from the Association of British Neurologists • We are unable to provide comment on this section. Comments from ERG • Assuming an average utility for a 65-year old is approximately 0.81, the company model implies the impact of stroke is a disutility of 0.28 and the impact of severe sialorrhoea is an additional disutility of 0.23, which the ERG finds unconvincing.
Technical team judgement after engagement	The technical team acknowledge that there are very limited utility data relating to drooling and that there is substantial uncertainty around both sets of utility values. It also acknowledges that it may be plausible that the "true" value lies between the two utility value sets. However, based on the current available evidence, the technical team prefer the EQ-5D data because it is derived from a population that reflects the intended treatment population more closely.

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Issue 4 – Ultrasound guidance

Questions for engagement	12. In clinical practice, would 100% of CBTA procedures include the use of ultrasound imaging?
Background/description of issue	In the SIAXI trial, approximately 55% of injections of CBTA were guided with the use of ultrasound imaging with all others being guided by anatomical landmarks. **The company** modelled the costs of the ultrasound imaging in its economic model based on the proportion of people that received ultrasound guided injections in the SIAXI trial, assuming this percentage was equivalent to NHS clinical practice. **The ERG** modelled a scenario where the costs of ultrasound imaging were included for all patients but did not include this in its base case. This was based on clinical expert opinion that all injections would be guided with ultrasound imaging.
Why this issue is important	Potential adverse events of CBTA may be severe with potential for risks associated with breathing and swallowing difficulty and ultrasound imaging may decrease this risk by ensuring accurate injection at the correct sites. For this reason, the full costs of treatment for all patients with ultrasound imaging should be considered.
Technical team preliminary judgement and rationale	Based on clinical expert opinion, **the technical team** agree that clinicians would use ultrasound guidance and it is more appropriate to include the costs of ultrasound guidance. The technical team are aware that this scenario only captures the cost of ultrasound guidance and does not represent the potential increase in efficacy of CBTA that may exist if ultrasound was used for all patients in SIAXI.
Summary of comments	Comments from company • Ultrasound guidance is used variably in UK clinical practice. • The proportion of patients modelled as receiving ultrasound guidance is equivalent to the number who received ultrasound guidance in the SIAXI trial.

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	• The assumption of all patients receiving ultrasound guidance has a limited impact on the cost-effectiveness results and may not take into account improved efficacy from using ultrasound imaging. Comments from Association of British Neurologists • Only a minority of cases would require ultrasound guidance. Comments from ERG • All ERG clinical experts believed that ultrasound guidance was likely to be used widely if CBTA was recommended.
Technical team judgement after engagement	The technical team acknowledge that there is variability in the use of ultrasound guidance in current clinical practice. Therefore, the company's assumption that the proportion of patients modelled as receiving ultrasound guidance is equivalent to the number who received ultrasound guidance in the SIAXI trial is appropriate. The technical team also acknowledge that the cost-effectiveness results are not sensitive to this assumption.

Issue 5 – Implementation

Questions for engagement	13. Are there any additional NHS resources required for treatment with CBTA? In particular: • Will clinicians require further training to administer CBTA injections? • Where is CBTA treatment currently provided in the NHS (specialist or non-specialist centres)? Is this likely to change if CBTA is recommended for sialorrhoea?
Why this issue is important	The administration costs of CBTA may require additional NHS resources such as training to administer CBTA injections and potentially regional-based centres may be required. This may have implications for implementing the guidance if CBTA for sialorrhoea is recommended as a treatment option within 3 months of the guidance being published.

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Technical team preliminary judgement and rationale	It is unclear what additional resource may be needed.
Summary of comments	Comments from company • CBTA is currently provided in specialist centres and this is unlikely to change if CBTA is recommended. • Training would be necessary, but the complexity and length of training would not be onerous. • CBTA is currently injected by a wide variety of healthcare professionals, no significant additional resource would be required on an individual centre basis. Comments from Association of British Neurologists • Some clinicians may need additional training for administering CBTA. • CBTA treatment is currently provided in secondary and tertiary care. Comments from ERG • Clinicians already trained in parallel clinical aspects of care would not find it onerous to be trained to inject CBTA. • Establishing a regional-based centre to perform CBTA injections would not be unrealistic.
Technical team judgement after engagement	The technical team acknowledge that clinicians would need additional training for administering CBTA for sialorrhoea. It remains unclear what additional resource cost this will incur and any implications for implementation if CBTA is recommended as an option.

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4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the Technical Report comments table provided.

Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate against standard of care

Alteration	Technical team rationale	ICER	Change from base case
Company base case	–	£9,583	-
1. ERG correction of minor errors	Technical team agreed with ERG's amendments, (see ERG report page 57)	£9,638	+£55
2. Utility values derived from SIAXI trial EQ-5D-3L data	Issue 3b	£47,309	+£37,726
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	–	£47,309	+£37,726

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Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Efficacy of glycopyrronium bromide	The company assumes that the efficacy of glycopyrronium bromide is 75% of CBTA because there is no available data for its effectiveness.	Unknown.
Anticholinergic treatments	No data is available for other anticholinergic treatments such as atropine sulphate or hyoscine hydrobromide. Glycopyrronium bromide is considered the most widely used treatment in NHS practice.	Unknown.
Adverse events	Adverse events were not modelled for either glycopyrronium bromide or CBTA because there was no available data, despite adverse events for both treatments being a concern to patients and clinicians.	Unknown.

Table 3: Other issues for information

Issue	Comments
Implementation of company model	The ERG highlighted a number of errors and judgements in the company model (relating to administration and acquisition costs, discontinuation scenarios, implementation of continuity correction, the standard mortality rates of people with sialorrhoea and the utility regression model). Correction of these errors increased the ICER by £55.
Innovation	The company considers the drug to be innovative. However, the technical team considers that all relevant benefits associated with the drug are adequately captured in the model.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

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