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


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| **Produced by** | School of Health and Related Research (ScHARR), The University of Sheffield |
| **Authors** | Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK |
| | Shijie Ren, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK |
| | Emma Simpson, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK |
| | Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK |
| | Martin Orr, Research Associate, ScHARR, University of Sheffield, Sheffield, UK |
| | Ruth Wong, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK |
| **Correspondence Author** | Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK |
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**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.

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**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.

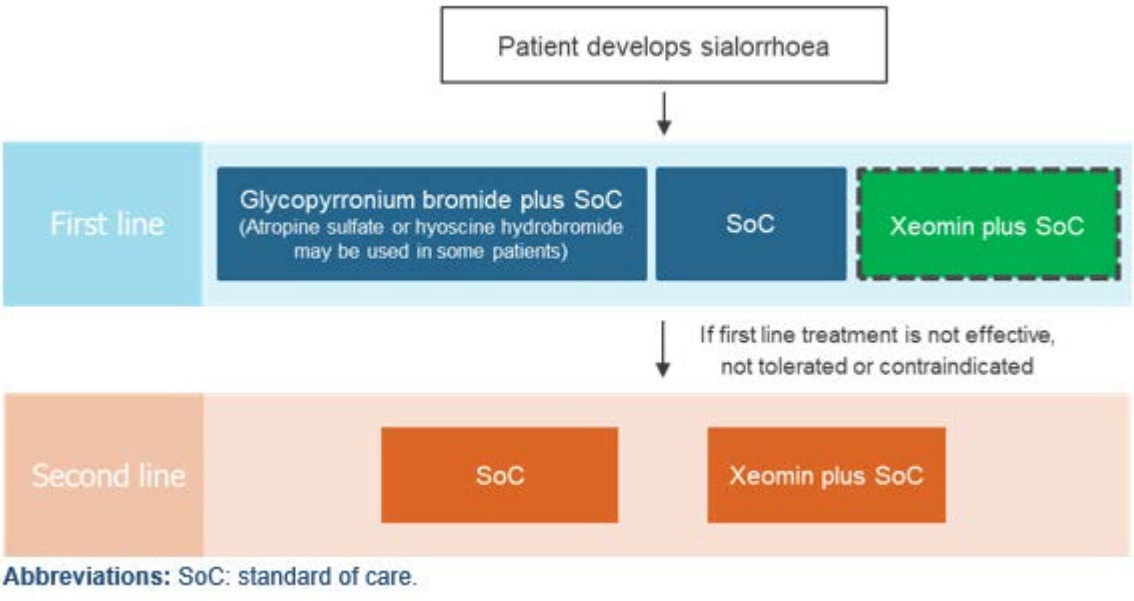
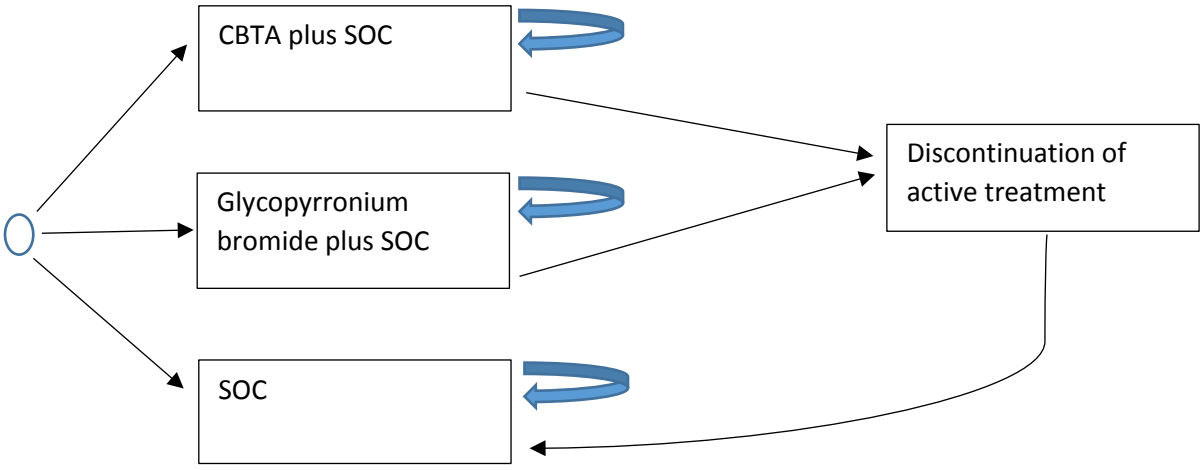



**Figure 1: The company's anticipated positioning of CBTA within the current clinical pathway**




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.<br>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).<br>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)<br>https://clinicaltrials.gov/show/nct02091739<br>2014.[6]<br><br>Blitzer 2017[8]<br>Blitzer 2018[9]<br>Jost 2018[10] | Phase III, prospective, randomised, double-blind, parallel-group, multicentre, Germany (53 patients) and Poland (131 patients)<br>Main period (MP) (16 weeks) placebo-controlled,<br>Extension period (EP) (48 weeks from end of MP) | Parkinson's Disease / Parkinsonism, stroke, TBI<br><br>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)<br><br>1) CBTA 100 U<br>N=74<br><br>2) CBTA 75 U<br>N=74<br><br>3) PBO<br>N=36 | Co-primary outcomes,<br>MP:<br>uSFR;<br>Global Impression of Change Scale (GICS) |
| NCT01653132<br>https://clinicaltrials.gov/show/nct01653132.<br>2012[11]<br><br>Narayanaswami 2016[12] | Phase II randomised, double-blind, placebo-controlled crossover trial, single centre, US-based | Parkinson's Disease / Parkinsonism<br><br>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<br>N=5<br><br>2) PBO followed by CBTA 100 U<br>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.<br>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).<br>The DSFS is the sum score of the two subscales, ranging from 2 (best) to a maximum (worst) score of 9.<br>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).<br>Treatment related adverse events (those considered related to treatment).<br>Adverse events of special interest (AESIs); those that possibly indicated toxin spread* (CS Section B.2.10).<br>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] | |
| LS-Mean difference versus placebo (SE) (95% CI) | [redacted] | | | |
| LS-Mean difference p-value | | | | |

| | | | | |
|---|---|---|---|---|
| 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.

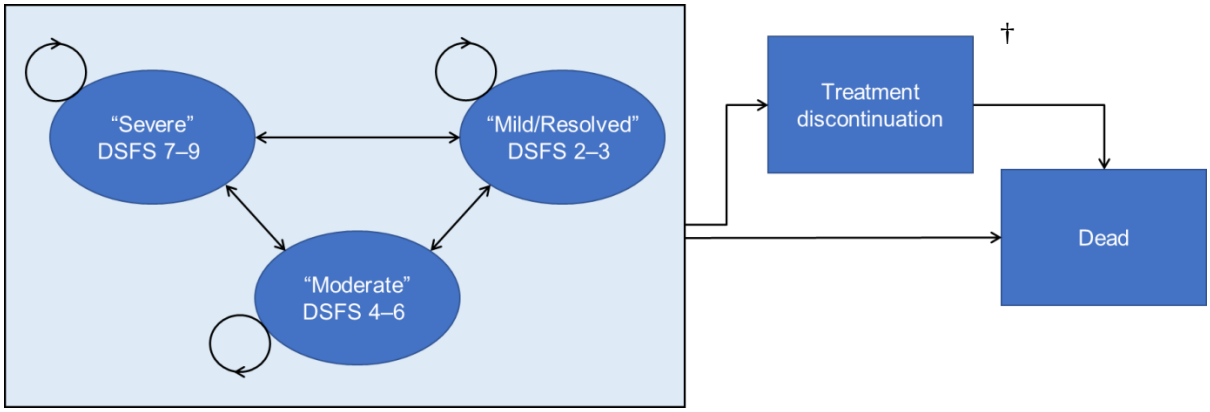
#### *4.2.3 Perspective, time horizon and discounting*

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

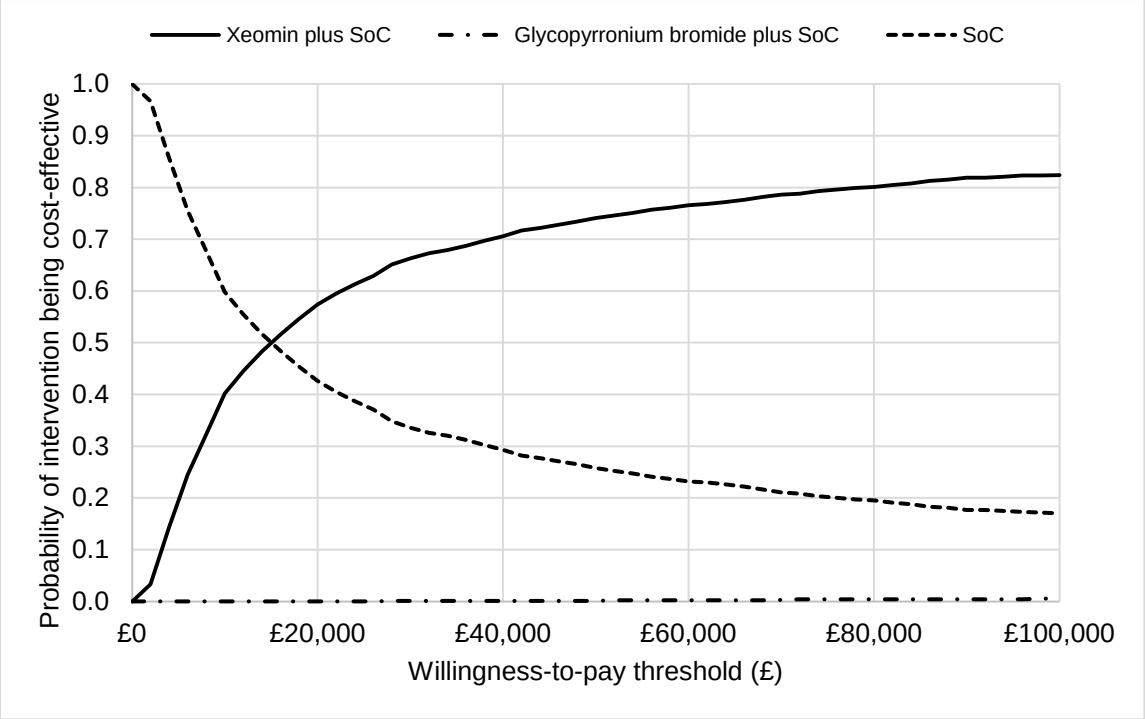



**Figure 4:** **Company's base case cost–effectiveness acceptability curve (adapted from modified base case results presented in responses to clarification questions)**

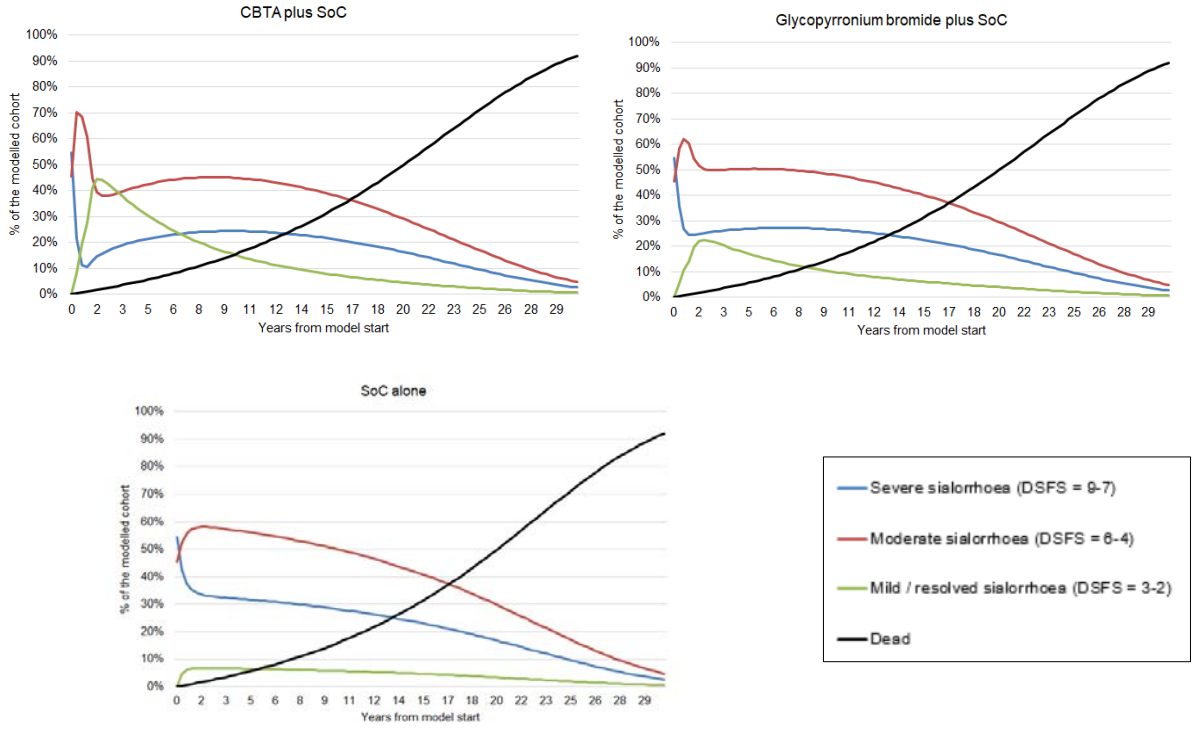



**Figure 5:** **Company's base case Markov trace graphs (adapted from modified base case results presented in responses to clarification questions)**

### *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.

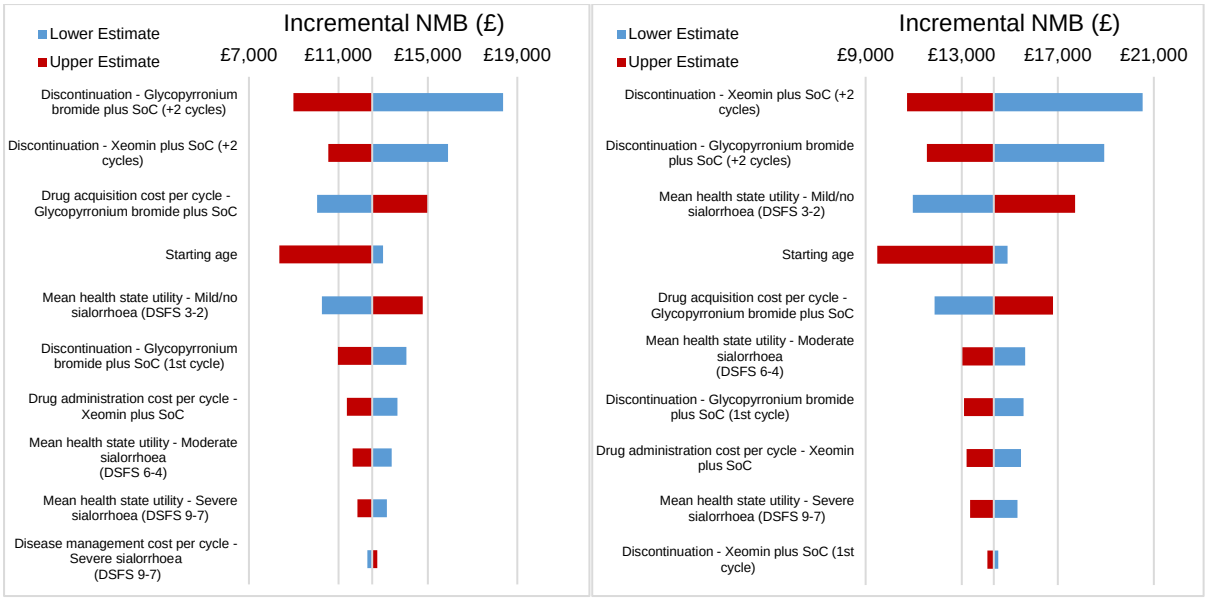



**Figure 6: CBTA plus SoC vs. glycopyrronium bromide plus SoC tornado plot with NMB calculated at (a) £20,000/QALY (on the left) (b) £30,000/QALY (on the right)**

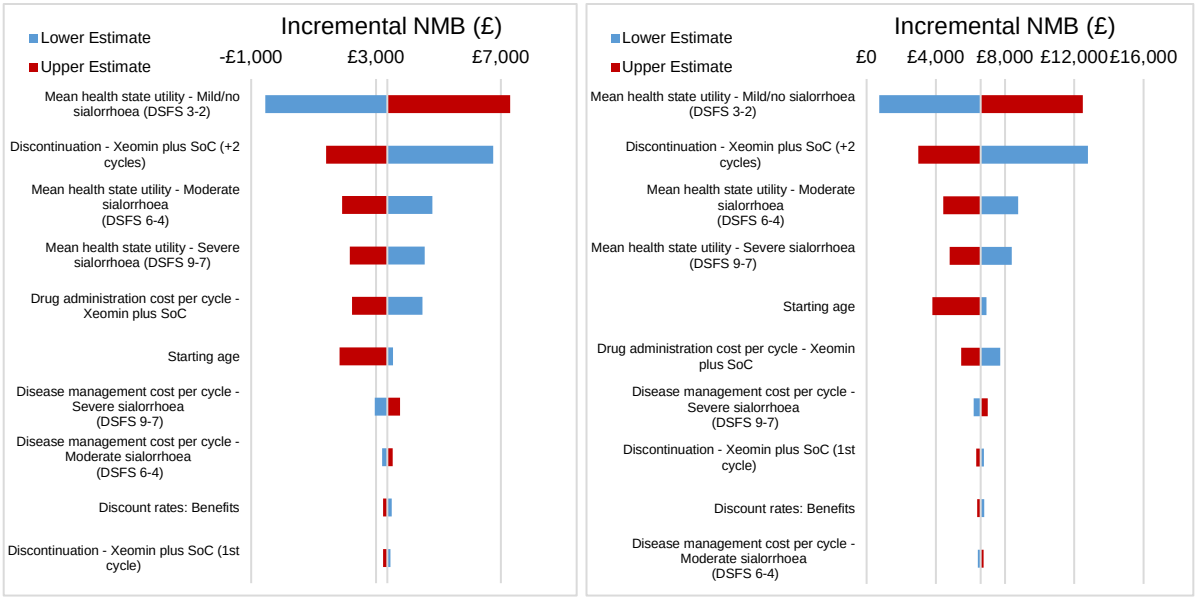



**Figure 7: CBTA plus SoC vs. SoC tornado plot with NMB calculated at (a) £20,000/QALY (on the left) (b) £30,000/QALY (on the right)**

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.

## 8 REFERENCES


1. Merz Pharma UK Ltd. Clostridium botulinum toxin A for treating chronic sialorrhoea [ID1150]. Company's evidence submission. 2019.
2. National Institute for Health and Care Excellence. NG62: cerebral palsy in under 25s. Available at: https://www.nice.org.uk/guidance/ng62 [Last accessed: 20 February 2019].
3. National Institute for Health and Care Excellence. NG42: motor neurone disease. Available at: https://www.nice.org.uk/guidance/ng42 [Last accessed: 9 October 2018].
4. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. 2013, https://www.nice.org.uk/process/pmg9/chapter/foreword [Last accessed: 20 February 2019].
5. National Institute for Health and Care Excellence. NG71: Parkinson's disease in adults. Available at: https://www.nice.org.uk/guidance/ng71 [Last accessed: 9 October 2018].
6. 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]. *Journal* 2014. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01544436/full [Last accessed: 20 February 2019]
7. Merz. SIAXI Interim Clinical Study Report (16th May 2017).
8. Blitzer A, Friedman A, Michel O, Flatau-Baque B, Csikos J, Merkel J, *et al.* Siaxi: incobotulinumtoxina for sialorrhea in parkinson's disease, stroke, and other etiologies-phase iii results. *Journal* 2017. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01439770/full [Last accessed: 20 February 2019]
9. Blitzer A, Friedman A, Michel O, Flatau-Baqué B, Csikós J, Jost W. SIAXI: IncobotulinumtoxinA for sialorrhea in Parkinson's disease, stroke, and other etiologies-Phase 3 Results. *Neurology* 2018;90.
10. Jost W, Friedman A, Michel O, Flatau-Baqué B, Csikós J, Blitzer A. 2018. SIAXI: Efficacy and safety of Xeomin (incobotulinumtoxinA) for the treatment of sialorrhea in Parkinson's disease (PD) and other neurological conditions: Results of a Phase III, placebo-controlled, randomized, double-blind study. Oral Presentation at the 70th American Academy of Neurology Annual Meeting, April 21-27, 2018, Los Angeles, United States of America. Presentation S.007.
11. ClinicalTrials.gov. Incobotulinum Toxin A (Xeomin®) for Troublesome Sialorrhea in Parkinson's Disease (PD)/Parkinsonism. Available at: https://clinicaltrials.gov/show/nct01653132 [Last accessed: 07 January 2019]. *Journal* 2012. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01478371/full [Last accessed: 20 February 2019]
12. Narayanaswami P, Geisbush T, Tarulli A, Raynor E, Gautam S, Tarsy D, *et al.* Drooling in Parkinson's disease: a randomized controlled trial of incobotulinum toxin A and meta-analysis of Botulinum toxins. *Journal* 2016. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01455316/full [Last accessed: 20 February 2019]
13. Centre for Reviews and Dissemination. CRD's guidance for undertaking reviews in health care. United Kingdom: CRD, University of York. 2009.
14. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org [Last accessed: 20 February 2019].
15. Ltd MPU. Clostridium botulinum toxin A for treating chronic sialorrhoea [ID1150]. Company's response to clarification questions from the ERG. 2019.
16. Narayanaswami P, Tarulli A, Raynor E, Gautam S, Geisbush T, Tarsy D. Randomized double-blind placebo-controlled cross-over study of incobotulinum toxin A for troublesome drooling in Parkinson's disease (PD). Poster Presentation:19th International Congress of the Movement Disorders Society. June 2015. Movement Disorders 2015:30: (Suppl 1) pp S203.

17. Food, Drug A. Prescribing Information: Xeomin (Incobotulinum toxin A). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125360s073lbl.pdf [Last accessed: 1 November 2018].
18. Office for National S. National life tables: England and Wales. Available at: https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandandwalesreferencetables/current/nltew1517reg.xls [Last accessed: 1st March 2019].
19. Hobson P, Meara J. Mortality and quality of death certification in a cohort of patients with Parkinson's disease and matched controls in North Wales, UK at 18 years: a community-based cohort study. *BMJ open* 2018;8:e018969.
20. Chang S-C, Lin C-K, Tung L-C, Chang N-Y. The association of drooling and health-related quality of life in children with cerebral palsy. *Neuropsychiatric disease and treatment* 2012;8:599-604.
21. Bird AM, Smith TL, Walton AE. Current treatment strategies for clozapine-induced sialorrhea. *The Annals of pharmacotherapy* 2011;45:667-75.
22. Arbouw M, Movig K, Koopmann M, Poels P, Guchelaar H, Egberts T, *et al.* Glycopyrrolate for sialorrhea in Parkinson disease: a randomized, double-blind, crossover trial. *Journal* 2010. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00742607/full [Last accessed: 20 February 2019]
23. European Medicines A. Sialanar 320 micrograms /ml oral solution (glycopyrronium bromide). Summary of Product Characteristics. Available at: https://www.ema.europa.eu/documents/product-information/sialanar-epar-product-information_en.pdf. [Last accessed: 19 May 2017].
24. Katzan IL, Dawson NV, Thomas CL, Votruba ME, Cebul RD. The cost of pneumonia after acute stroke. *Neurology* 2007;68:1938-43.
25. Mato A, Limeres J, Tomás I, Muñoz M, Abuín C, Feijoo JF, *et al.* Management of drooling in disabled patients with scopolamine patches. *British journal of clinical pharmacology* 2010;69:684-8.
26. Net Monetary Benefit [online]. (2016). York; York Health Economics Consortium; 2016. https://www.yhec.co.uk/glossary/net-monetary-benefit/ [Last accessed: 20 February 2019].
27. Ara R, Brazier JE. Populating an Economic Model with Health State Utility Values: Moving toward Better Practice. *Value in Health* 2010;13:509-18.
28. Hernández Alava M, Wailoo AJ, Ara R. Tails from the peak district: adjusted limited dependent variable mixture models of EQ-5D questionnaire health state utility values. *Value in Health* 2012;15:550-61.
29. NHS Digital. Prescription Cost Analysis: England. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis [Last accessed: 8th April 2019].
30. Wailoo AJ, Hernandez-Alava M, Manca A, Mejia A, Ray J, Crawford B, *et al.* Mapping to Estimate Health-State Utility from Non-Preference-Based Outcome Measures: An ISPOR Good Practices for Outcomes Research Task Force Report. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2017;20:18-27.

# 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

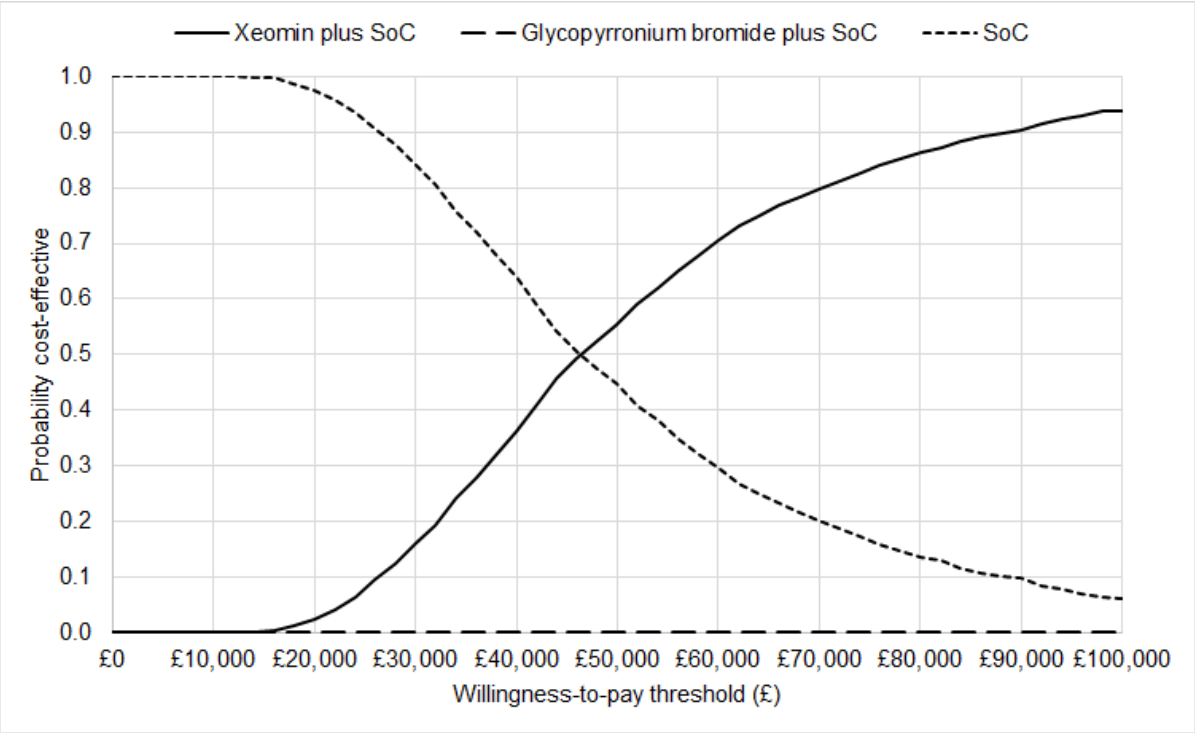



**Figure 8: ERG's base case cost–effectiveness acceptability curve (severe patients)**

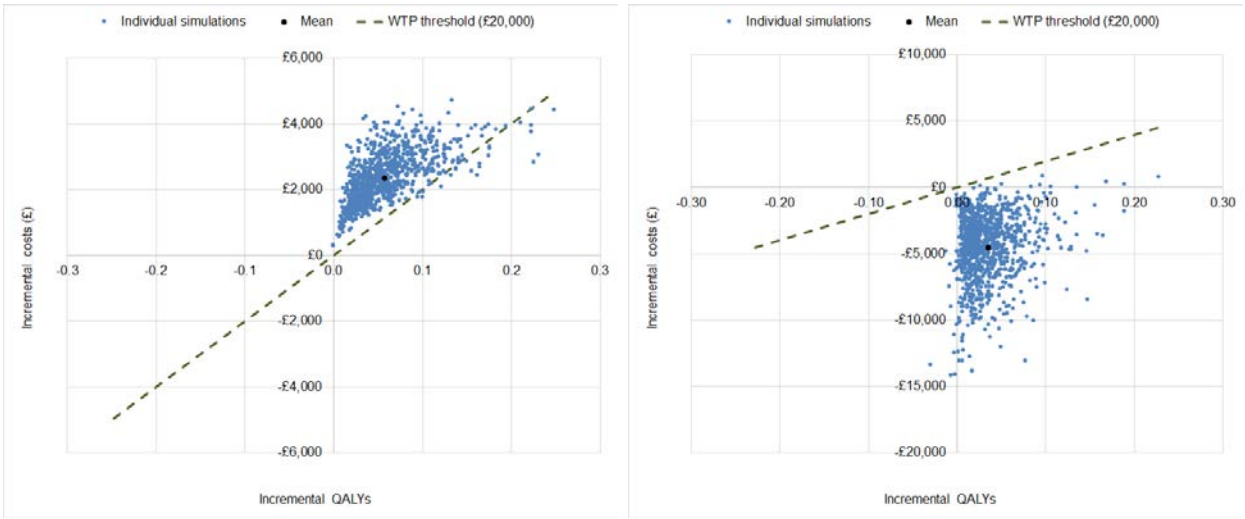



**Figure 9: ERG's cost-effectiveness planes of CBTA + SoC (severe patients) versus (i) SoC alone (left side) (ii) glycopyrronium bromide (right side)**

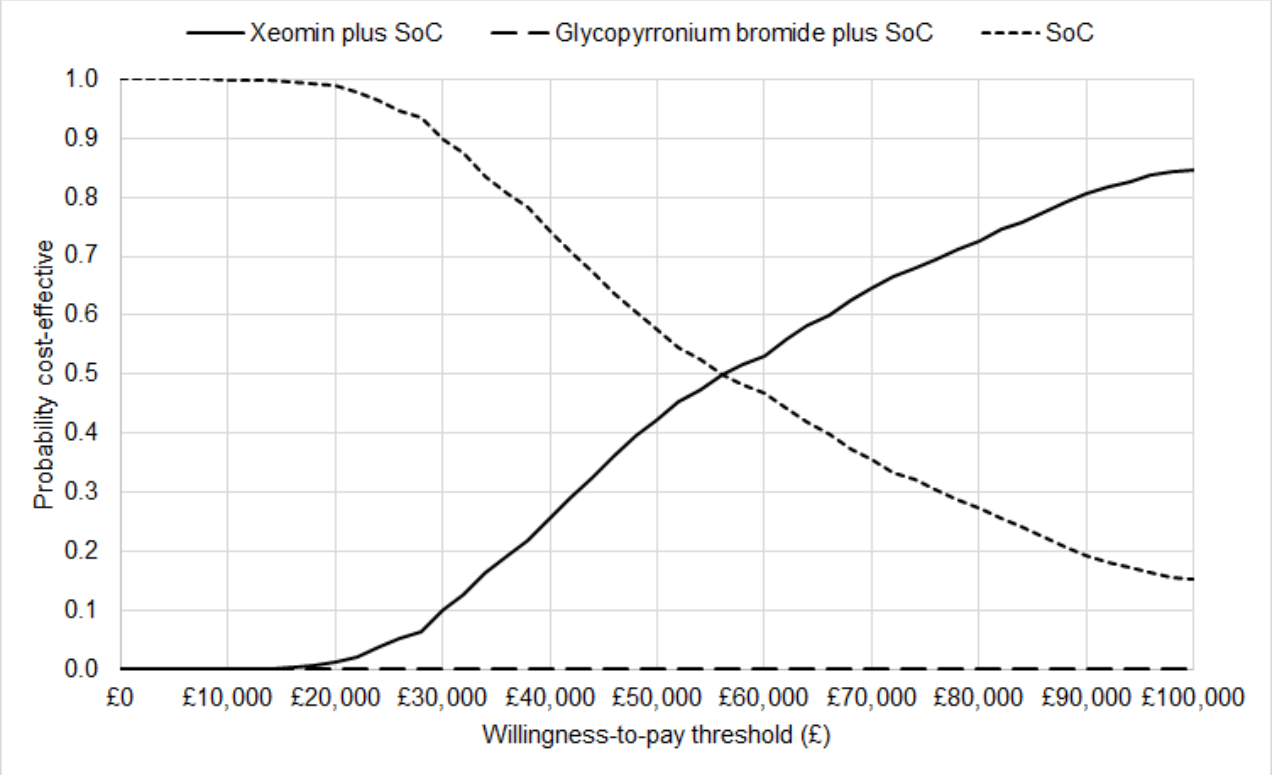



**Figure 10: ERG's base case cost–effectiveness acceptability curve (moderate patients)**

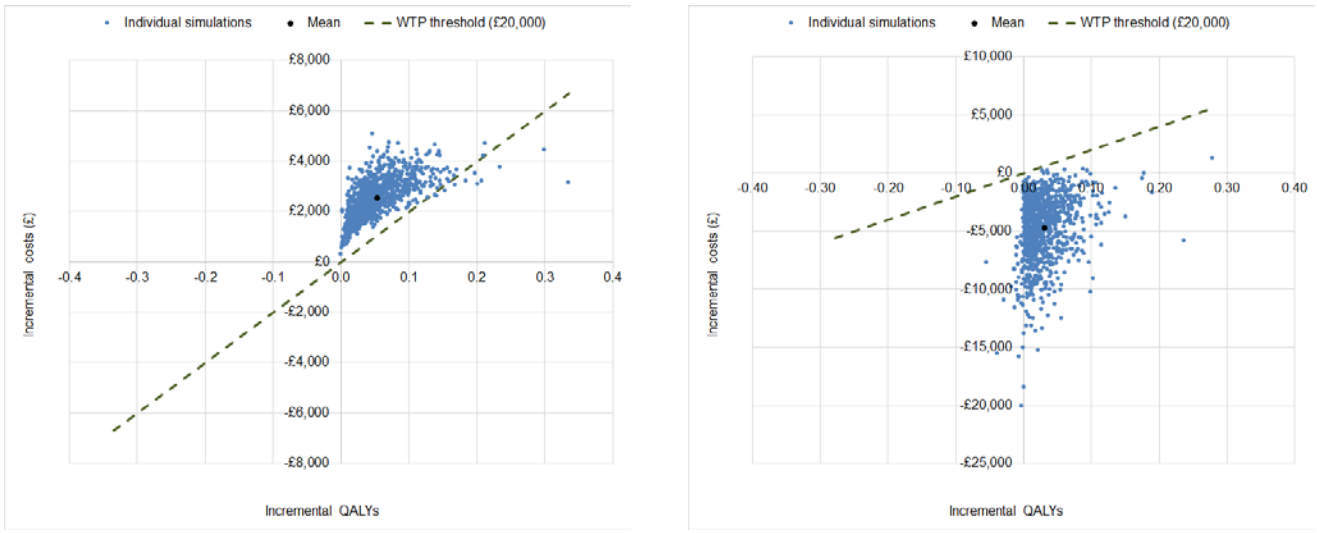



**Figure 11: ERG's cost-effectiveness planes of CBTA + SoC (moderate patients) versus (i) SoC alone (left side) (ii) glycopyrronium bromide (right side)**

## Appendix 3: ERG's one-way sensitivity analyses (tornado plots) at the £20,000/QALY threshold

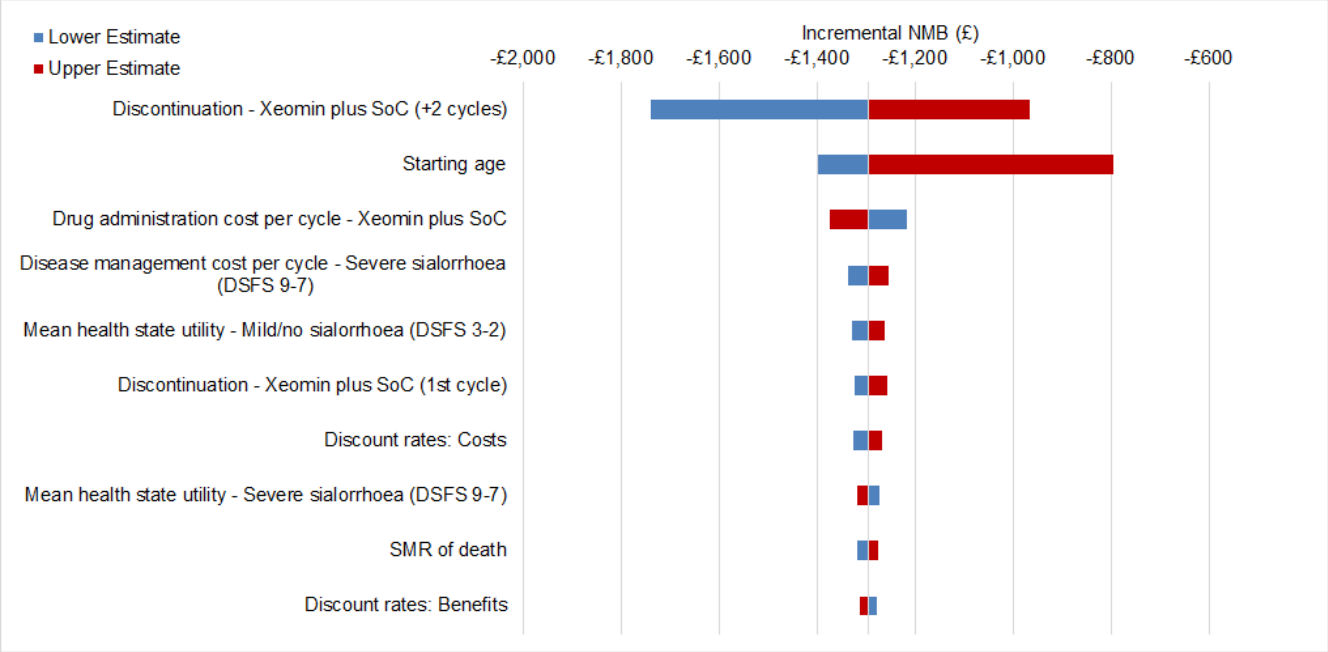



**Figure 12: CBTA plus SoC vs. SoC tornado plot (ERG base case - severe patients)**

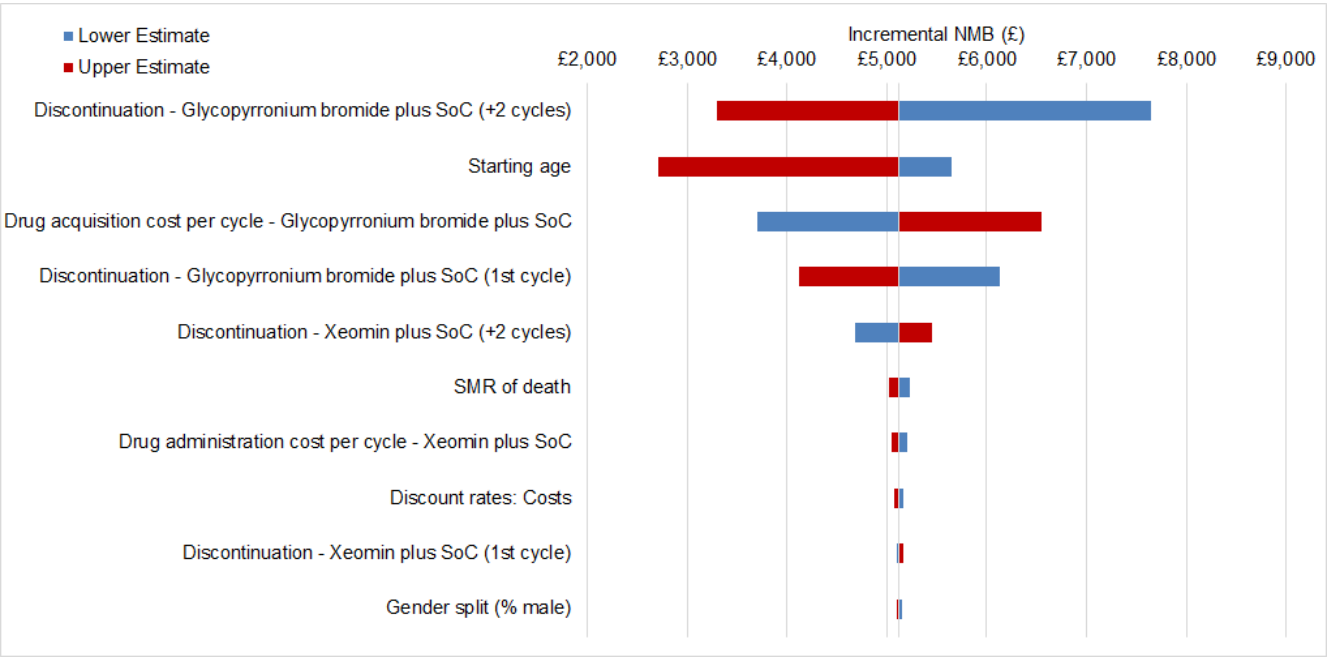



**Figure 13: CBTA plus SoC vs. glycopyrronium bromide tornado plot (ERG base case - severe patients)**

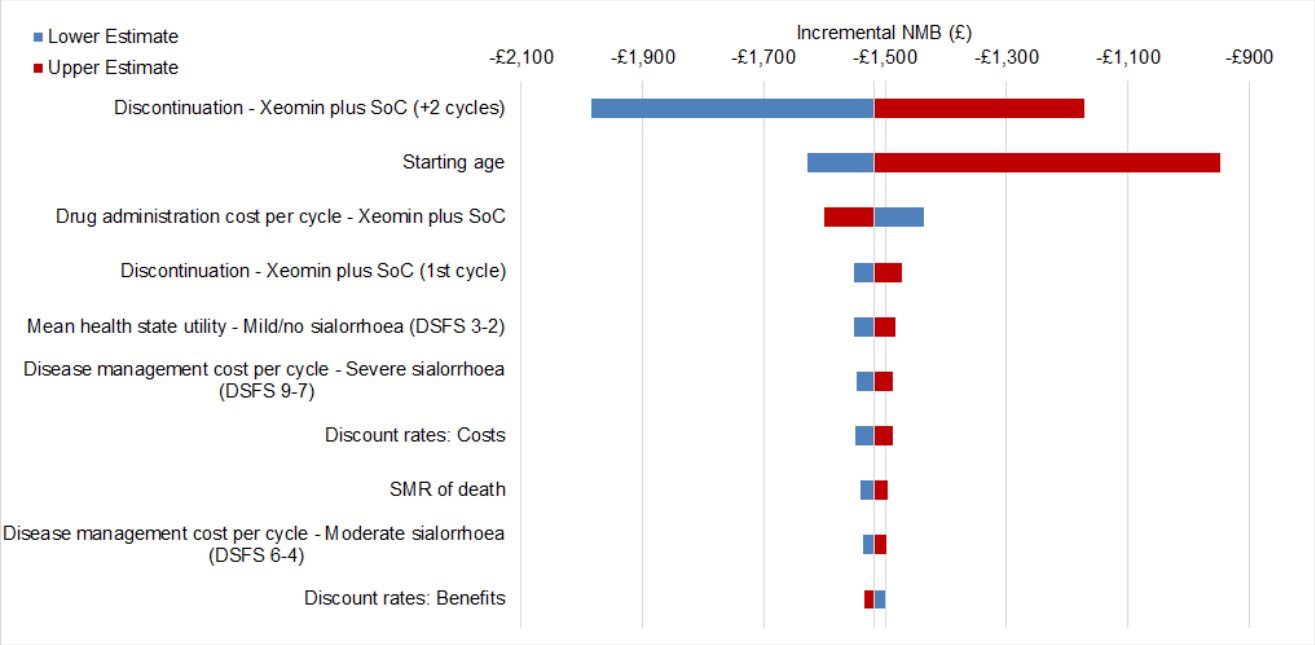



**Figure 14: CBTA plus SoC vs. SoC tornado plot (ERG base case - moderate patients)**

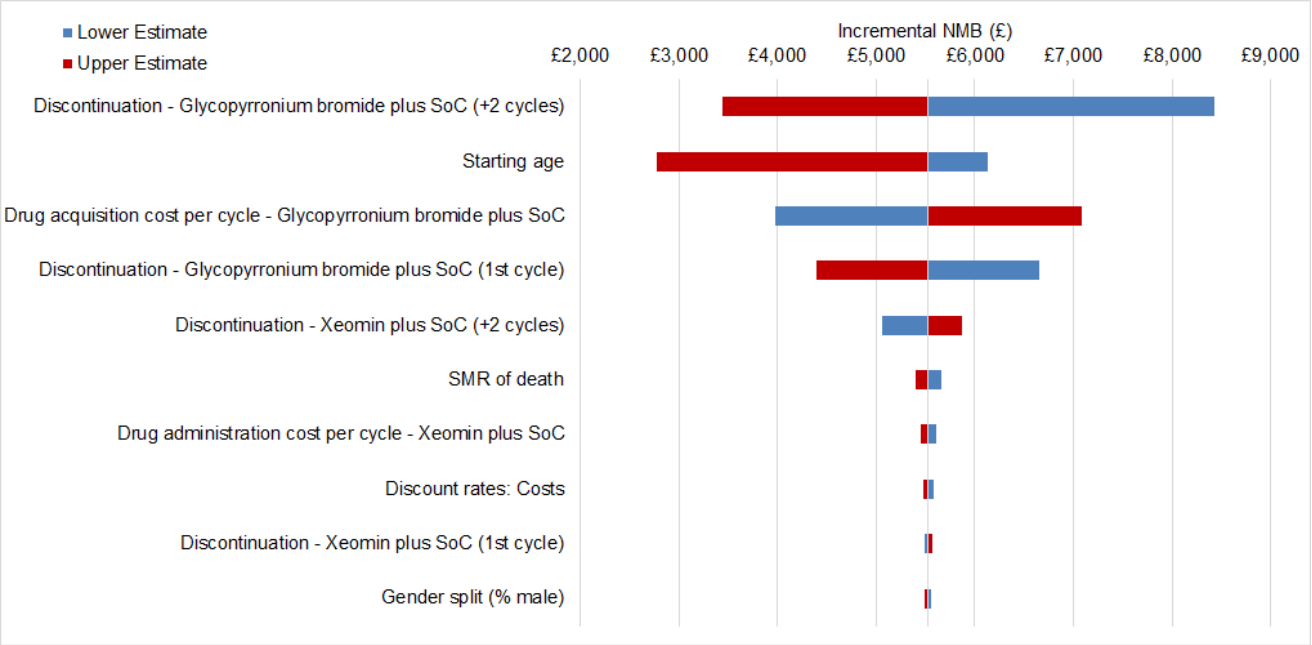



**Figure 15: CBTA plus SoC vs. glycopyrronium bromide tornado plot (ERG base case - moderate patients)**

## Appendix 4: ERG's one-way sensitivity analyses (tornado plots) at the £30,000/QALY threshold

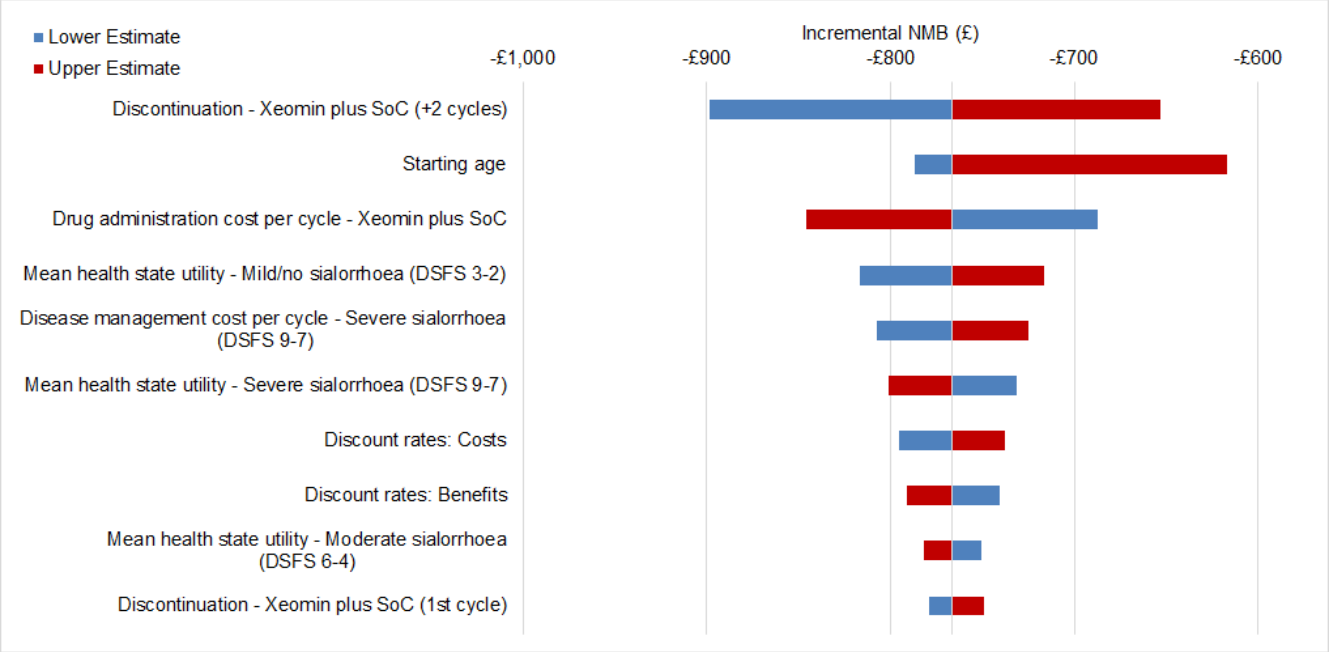



**Figure 16: CBTA plus SoC vs. SoC tornado plot (ERG base case - severe patients)**

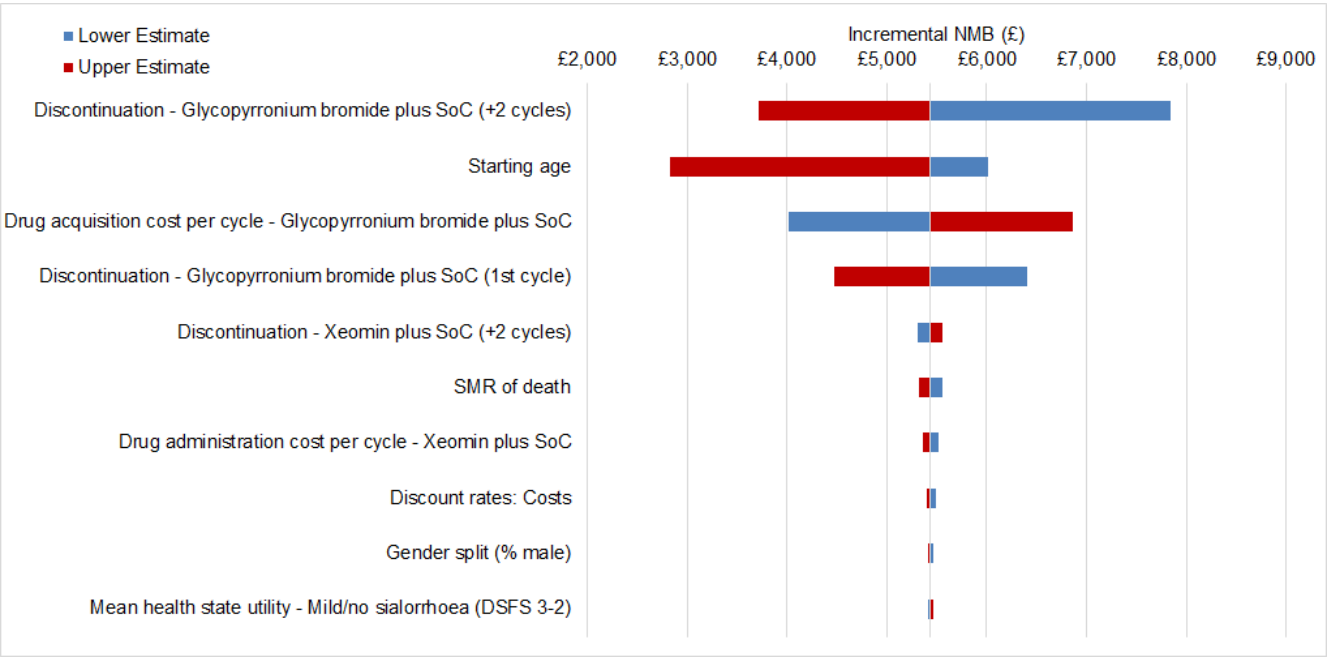



**Figure 17: CBTA plus SoC vs. glycopyrronium bromide tornado plot (ERG base case - severe patients)**

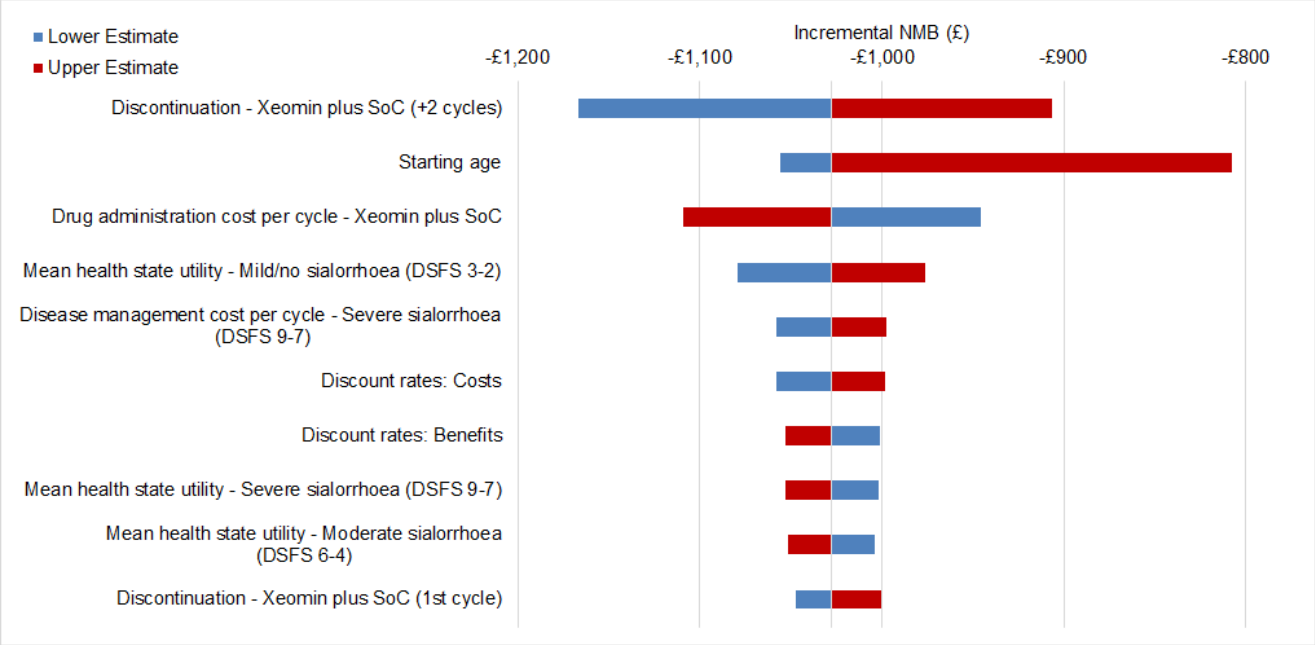



**Figure 18: CBTA plus SoC vs. SoC tornado plot (ERG base case - moderate patients)**

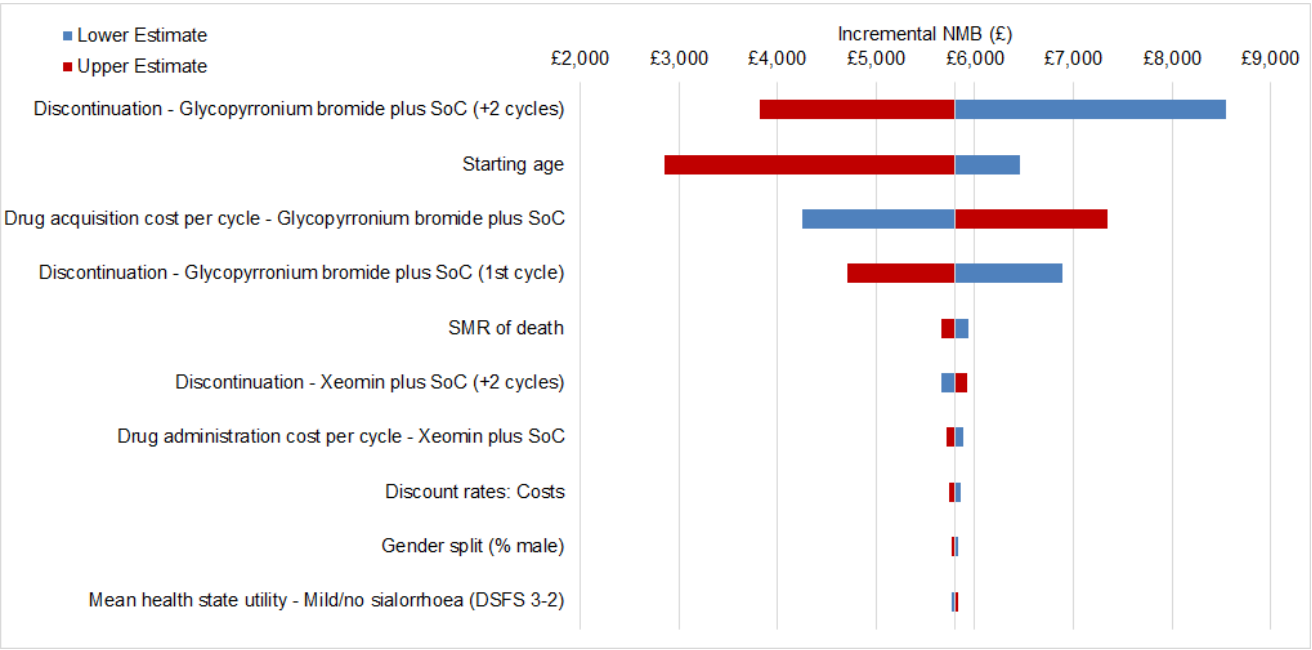



**Figure 19: CBTA plus SoC vs. glycopyrronium bromide tornado plot (ERG base case - moderate patients)**