NICE National Institute for Health and Care Excellence

Slides for handouts – redacted

Clostridium botulinum toxin A for chronic sialorrhoea [ID1150]

Lead team presentation

Lead team: Olaolu Oloyede, Matt Bradley, Rebecca Harmston

ERG: ScHARR – University of Sheffield

Technical team: Gary McVeigh, Adam Brooke, Nicola Hay, Linda Landells

Company: Merz Pharma

24th July 2019

Disease background

- Sialorrhoea is the inability to control oral secretions resulting in excessive saliva accumulation
- Inconsistently defined term, could mean:
  - **Drooling –** uncontrollable loss of saliva from the mouth (anterior loss)
  - **Hypersalivation –** excess production of saliva from parotid, submandibular and sublingual glands
- Common symptom of many neurological conditions
- Ineffective swallowing, inadequate rate of swallowing and poor lip seal are considered primary causes of sialorrhoea for many neurological conditions such as Parkinson's disease
- Additional burden of sialorrhoea with underlying neurological condition includes:
  - Psychosocial impact
  - Risk of aspiration pneumonia
  - Other consequences from accumulation of saliva

Patient perspective

Overview

- Estimated eligible population of around 47,000 with diverse neurological conditions such as Parkinson's disease, stroke, cerebral palsy, motor neurone disease and traumatic brain injury – some of these conditions are more prevalent in older people

Symptoms

- Psychosocial impact – social embarrassment, decreased self-esteem, social isolation
- Oral hygiene – perioral dermatitis, bad breath, increased bacteria
- Sleep disturbance, dehydration, fatigue, stress and anxiety
- Risk of aspiration pneumonia if saliva is inhaled (5–10% of patients)
- Caregiver burden of managing drooling – wellbeing of carers decreases over time

Current experience of treatment

- Variable psychosocial impact dependent on age, severity and condition
- Standard of care involves bibs as well as speech, language and occupational therapy
- Some pharmacological management options available and intervention in this appraisal is sometimes available as a second line treatment
- Effective management of sialorrhoea can mean the ability to live at home for longer

Clostridium botulinum toxin A (CBTA) (Xeomin, Merz)

Mechanism	• Blocking surrounding nerves that control saliva production in the parotid and submandibular salivary glands
Marketing authorisation	• CHMP positive opinion May 2019: “treatment of adults with chronic sialorrhoea due to neurological conditions”
Administration and dose	• 100 units per administration injected into the parotid and submandibular glands
List price	• £129.90 per 100 unit vial (£422.18 annual cost)

Other indications	• Xeomin is indicated for blepharospasm, cervical dystonia of a predominantly rotational form (spasmodic torticollis) and spasticity of the upper limbs in adults
	• Other CBTA and CBTB products are indicated for:
	  • Focal spasticity
	  • Chronic migraine
	  • Bladder disorders
	  • Skin and skin appendage disorders

Decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission
Population	Adults with chronic sialorrhoea	As per final scope
Intervention	CBTA with standard care	As per final scope
Comparator	• Anticholinergic drugs such as glycopyrronium bromide For people in whom anticholinergic drugs are unsuitable: • Established clinical management	• Glycopyrronium bromide For people in whom anticholinergic drugs are unsuitable: • Standard of care (SoC; basic non-pharmacological management)
Outcomes	The outcome measures to be considered include: - Unstimulated salivary flow rate - Response rates - Adverse effects of treatment - Health-related quality of life	Additional including: • Global impression of change scale (GICS) • Drooling severity and frequency score (DSFS)

[redacted]

Professional group comments

Aims of treatment
- Reduce excess saliva production, which results in unpleasant dribbling onto clothes and irritation at the corners of the mouth

Current treatment options
- Limited – anticholinergic therapy can cause cognitive and neuropsychiatric problems, particularly when there is cognitive impairment

Clinical need
- Need for a targeted treatment that avoids systemic side effects
- Not required in most patients

Informal stopping rules
- Lack of benefit assessed by adjusting doses and sites over 3 consecutive treatment cycles and deciding if benefit is evident – stopping if not
- Some patients become immune to CBTA and there is an option to try CBTB
- Also stopped if significant side effects develop

[redacted]

Key clinical evidence - SIAXI trial

- Phase III randomised, double-blind, multicentre study in Germany and Poland
- Sialorrhoea aetiology (79% Parkinson's related, 18% stroke, 3% traumatic brain injury)
- Main period - randomised 2:1 CBTA (100 units):placebo for 16 weeks (1 cycle)
- Extension period without placebo for 64 weeks (further 3 cycles)

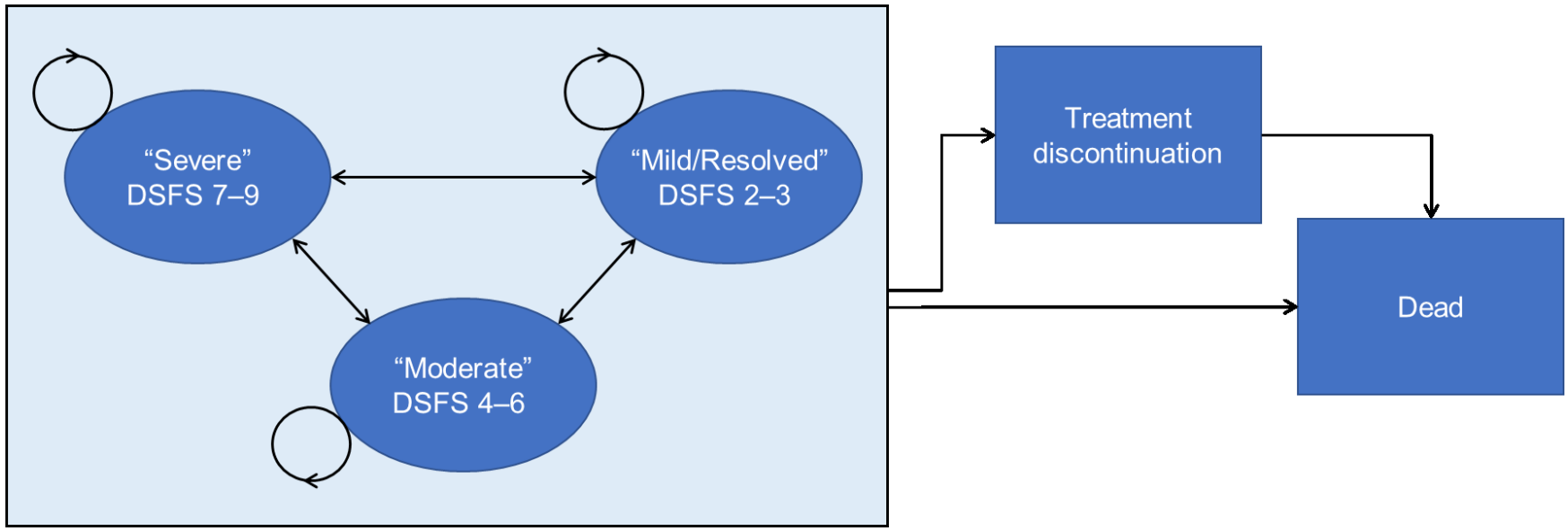
Outcomes		Main period (weeks)				Extension period (cycle)		
		4	8	12	16	2	3	4
Mean change in unstimulated salivary flow rate from baseline	CBTA	-0.13	-0.13	-0.12	-0.11	[redacted]	[redacted]	[redacted]
	PLA	-0.04	-0.02	-0.03	-0.01			
Global impression of change scale	CBTA	1.25	1.30	1.21	0.93	[redacted]	[redacted]	[redacted]
	PLA	0.67	0.47	0.56	0.41			
Drooling severity and frequency scale	CBTA	-1.66	-1.97	-1.62	-1.18	[redacted]	[redacted]	[redacted]
	PLA	-0.50	-0.68	-1.00	-0.75			
EQ-VAS	CBTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA	[redacted]	[redacted]	[redacted]	[redacted]			

[redacted] Significant difference ($p<0.05$) vs placebo

*since previous injection

Economic model structure

State transition Markov model



- 3 health states defined by DSFS score
- Baseline DSFS score from SIAXI baseline
- Patients can transition between any state
- Patients that discontinue revert to baseline*
- Any state can independently transition to death

- Time horizon: 10 years
- 3.5% discount rate
- NHS/PSS perspective
- 16-week cycle length

[redacted]

*updated at clarification stage

Model assumptions

Comparators	• CBTA with standard of care compared with:
	  • glycopyrronium bromide with standard of care
	  • standard of care alone
	• Costs of atropine sulfate and hyoscine hydrobromide considered in scenario analysis

Source of QALY gain	• No excess mortality modelled in company base case, all QALY gains are from increased health-related quality of life • Alternative standardised mortality rates explored in scenario analysis
Adverse events	• No adverse events modelled due to lack of data
Utilities	• Company base case uses estimated utility values from NG62 guideline stratified into 3 health states based on DSFS • Company considers EQ-5D to be insensitive to sialorrhoea-related changes in quality of life in the SIAXI population
Costs and resource use	• All drug costs at list prices on BNF • Administration costs based on NHS outpatient reference cost and ultrasound scan for the same % as received a scan in SIAXI • Other health-state costs based on NHS speech pathology and occupational therapy consultation costs, assumes twice as many visits for severe patients compared to moderate patients

Issues resolved after technical engagement

	Summary of original issue	Engagement response	Technical team judgement	Issue resolved?
1a	Company positioned CBTA as first line treatment for all patients with sialorrhoea regardless of underlying neurological condition	The mechanism of action does not depend on underlying neurological condition that causes sialorrhoea	It is appropriate to assume equal efficacy for all eligible population	**Partially**
1b	Company modelled mixed moderate / severe patient population (by DSFS) Company did not model a stopping rule including possibility of immunity to CBTA	Severe sialorrhoea is not a distinct subgroup and severity can fluctuate There are no formal stopping rules and no evidence that immunity would cause loss of response	It is inappropriate to limit treatment options based on severity in this disease area. Treatment choice is also based on other considerations Concerns about potential immunity have been resolved	**Partially**

[redacted]

Outstanding issues after technical engagement

- **Issue 1: Comparators and treatment choice**

  (slides 12-14)
- **Issue 2: Outcomes**

  (slides 15-16)
- **Issue 3: Health-related quality of life and utility value source**

  (slides 17-20)
- **Issue 4: Ultrasound guidance**

  (slide 21)
- **Issue 5: Implementation**

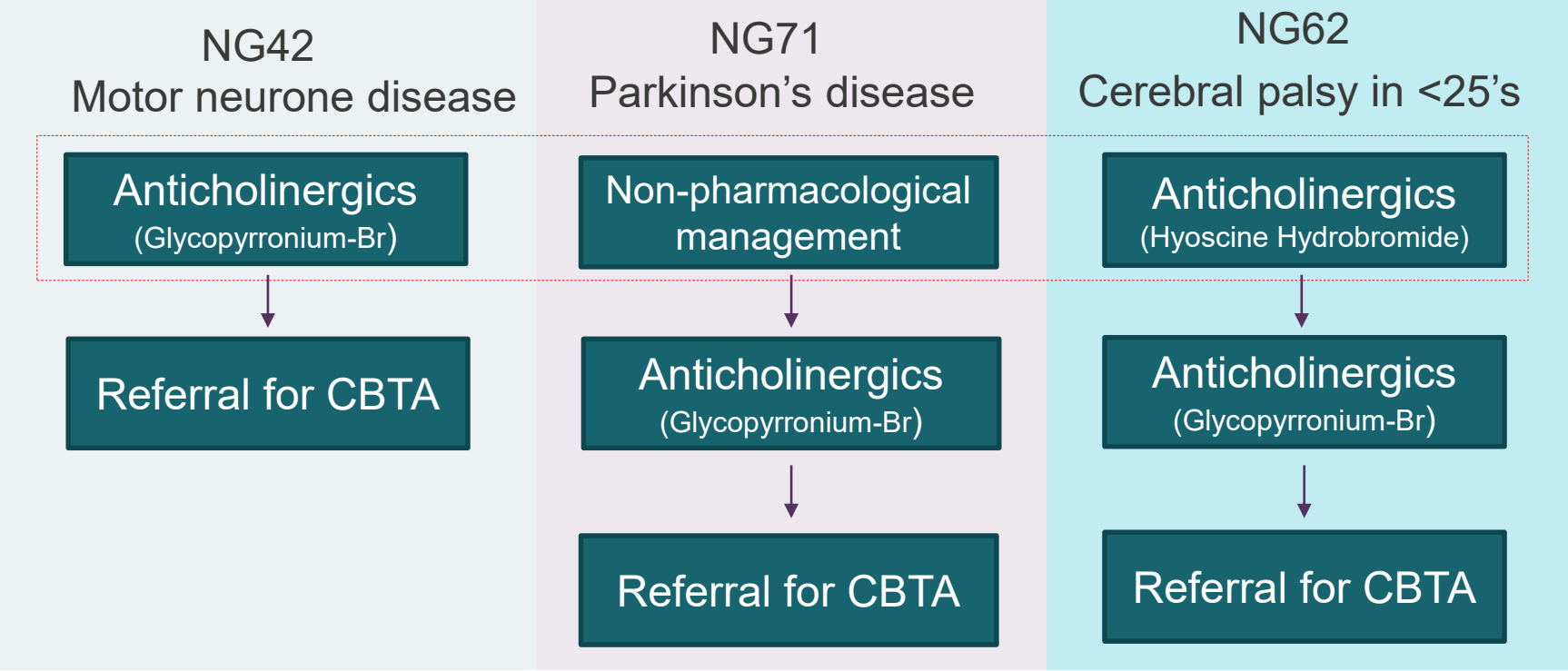
  (slide 22)
- **Issue 6 : Resource use – (new since technical report)**

[redacted]

Issue 1: Comparators and treatment choice

Background

- Company has positioned CBTA as a broad first-line treatment across sialorrhoea aetiologies
- Company consider standard of care and anticholinergics (primarily glycopyrronium bromide) in base case analysis (+ hyoscine hydrobromide and atropine sulphate in scenario analysis)



- Choice of active treatment over standard of care may depend on co-morbidities, severity of disease, efficacy of previous treatment and patient/clinician choice

[redacted]

Issue 1: Comparators and treatment choice

Background

- Treatment options for sialorrhoea are limited
- Anticholinergics are the alternative to SoC but are poorly tolerated, adverse events including dry mouth, falls, dizziness and potential cognitive decline
- These adverse events can cause major problems for older people
- Glycopyrronium bromide is the preferred anticholinergic because it does not cross the blood-brain barrier and therefore is one of the most routinely used anticholinergics
- Glycopyrronium bromide has a marketing authorisation for severe sialorrhoea in children and adolescents aged 3 years and older with chronic neurological conditions
- The summary of product characteristics states that duration of glycopyrronium bromide use should be as short as possible, intermittent use for chronic diseases
- Many clinicians do not use in people aged over 65 and there are high drop-out rates
- Many patients do not receive any active treatment because of these issues with anticholinergics

Preliminary judgement

- Glycopyrronium bromide is the most appropriate pharmacological comparator
- Standard of care is also an appropriate comparator for those that cannot take anticholinergics

[redacted]

Issue 1: Comparators and treatment choice

Company response

- Current clinical practice aligns with NICE guidelines
- The mechanism of action means CBTA avoids polypharmacy which is prevalent in these neurological conditions and adverse events associated with systemic treatments
- CBTA is positioned as a first-line active treatment when SoC is inadequate

ERG comments

- Lack of clinical evidence and incidence of adverse events limit the use of anticholinergics, despite NICE recommendations in clinical guidelines
- ERG's clinical experts advised that if a CBTA product was licensed at the time of writing the guidelines, it would have been recommended at first-line over anticholinergics

Final technical report judgement

- If approved, CBTA is likely to displace anticholinergic use at first-line treatment
- CBTA will also displace standard of care for a considerable amount of people for whom anticholinergics are intolerant or contraindicated
- Treatment with glycopyrronium bromide is intermittent and used for a short amount of time
- The SIAXI trial compares with standard of care and an indirect treatment comparison was not possible because of lack of evidence
- For these reasons, standard of care is the most appropriate comparator for most patients but consideration will be given to glycopyrronium bromide as the comparator in the short term

Issue 2: Outcomes

Background

- The following clinical outcomes were measured in the SIAXI trial:

Co-primary outcomes

Unstimulated salivary flow rate (uSFR)

Calculated by swab method – weight of 4 absorbent rolls placed at the orifices of the salivary glands over 5-minute period (g/min)

Unclear if there is association with health-related quality of life

Global Impression of Change (GICS)

7-point Likert scale from −3 (much worse) to +3 (much improved) asked about function compared with time of last injection.

Secondary outcome used in economic model

Drooling Severity and Frequency Scale (DSFS)

Two subscales added together:

- A 4-point Likert scale for drooling frequency 1 (never) to 4 (constantly)
- A 5-point Likert scale for drooling severity 1 (dry) to 5 (profuse)

Not validated with health-related quality of life and unclear if there is association

Transitions between DSFS states modelled in the economic analysis

[redacted]

Issue 2: Outcomes

Preliminary judgement

- No survival benefit is modelled so the outcome must correlate with health-related quality of life to model QALY gain
- EQ-5D was also measured in the trial, it may be most appropriate to directly model health-related quality of life benefit from EQ-5D measurements

Company response

- DSFS is the most appropriate measure of disease severity which correlates well with the disease burden associated with sialorrhoea

Association of British Neurologists comments

- Scoring systems are not part of standard clinical practice, sialorrhoea is measured by physical examination and a detailed history from the patient and carers

Final technical report judgement

- None of the clinical outcomes measured in the trial are used in clinical practice
- DSFS may be the most relevant clinical outcome for disease severity because subjective drooling accounts for most of the disease burden
- EQ-5D is the most appropriate measure of health-related quality of life (see Issue 3), although DSFS can be used to inform measurement of disease severity in the model

[redacted]

Issue 3: HRQoL and utility values

Background

- Symptoms associated with sialorrhoea include poor oral hygiene, bad breath, eating and speaking difficulty, sleep disturbance, dehydration, the risk of aspiration pneumonia and psychosocial impact
- These symptoms may have different impact depending on subjective response and underlying neurological condition – there are few sources of utility data for people with sialorrhoea
- EQ-5D-3L measured in trial but company states that this is insensitive to measuring symptoms of sialorrhoea because of the context of debilitating underlying neurological conditions
- EQ-5D-3L can only register a change in patient utility value where a patient indicates a step change in at least one domain – most patients in the SIAXI trial enrolled answered “some problems” for the 5 domains at baseline

	Mobility	Self-care	Usual activities	Pain	Anxiety/ depression
Responded with a score of 2 “some problems”	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- Patients would need to feel able to answer 1 “no problems” to register any improvement
- [redacted]

[redacted]

Issue 3: HRQoL and utility values

Background

- Company proposed using utility values from NG62 guideline for cerebral palsy in under 25s stratified by DSFS severity into 3 groups
- ERG used a regression model (that allows for repeated measures, does not assume equal weight for the scores in each severity category) using EQ-5D-3L data from the SIAXI trial

	ERG model (SIAXI EQ-5D-3L data)	Company model (NG62-derived values)
Resolved / Mild (DSFS 2-3)	0.6227	0.5346
Moderate (DSFS 4-6)	0.5983	0.4283
Severe (DSFS 7-9)	0.5774	0.3008

Preliminary judgement

- Technical team preferred EQ-5D-3L data and utility values derived from the SIAXI trial because this was consistent with the NICE reference case
- Acknowledged that it is possible that the EQ-5D-3L does not capture fully the impact of sialorrhoea on a patients quality of life

[redacted]

Issue 3: HRQoL and utility values

Company response

- There is uncertainty about measurement of health-related quality of life but the “true” utility values likely lie between the company and ERG utility values
- Also not captured by EQ-5D: caregiver burden, psychosocial impact from social isolation, potential for aspiration pneumonia in 5-10% of people with sialorrhoea (not measured in trial)

Association of British Neurologists comments

- It is unlikely that any of the specific consequences of sialorrhoea would be reliably detected in a non-saliva specific questionnaire

ERG comments

- NG62 guideline population is strikingly different from the SIAXI trial, utility data from NG62 should not take primacy over trial data. Not convinced impact of sialorrhoea (-0.23) would be similar magnitude as the impact of the underlying neurological condition (-0.28).
- Not convinced by empirical evidence on lack of content validity of the EQ-5D
- The EQ-5D-3L may be accurately picking up a small utility gain associated with sialorrhoea

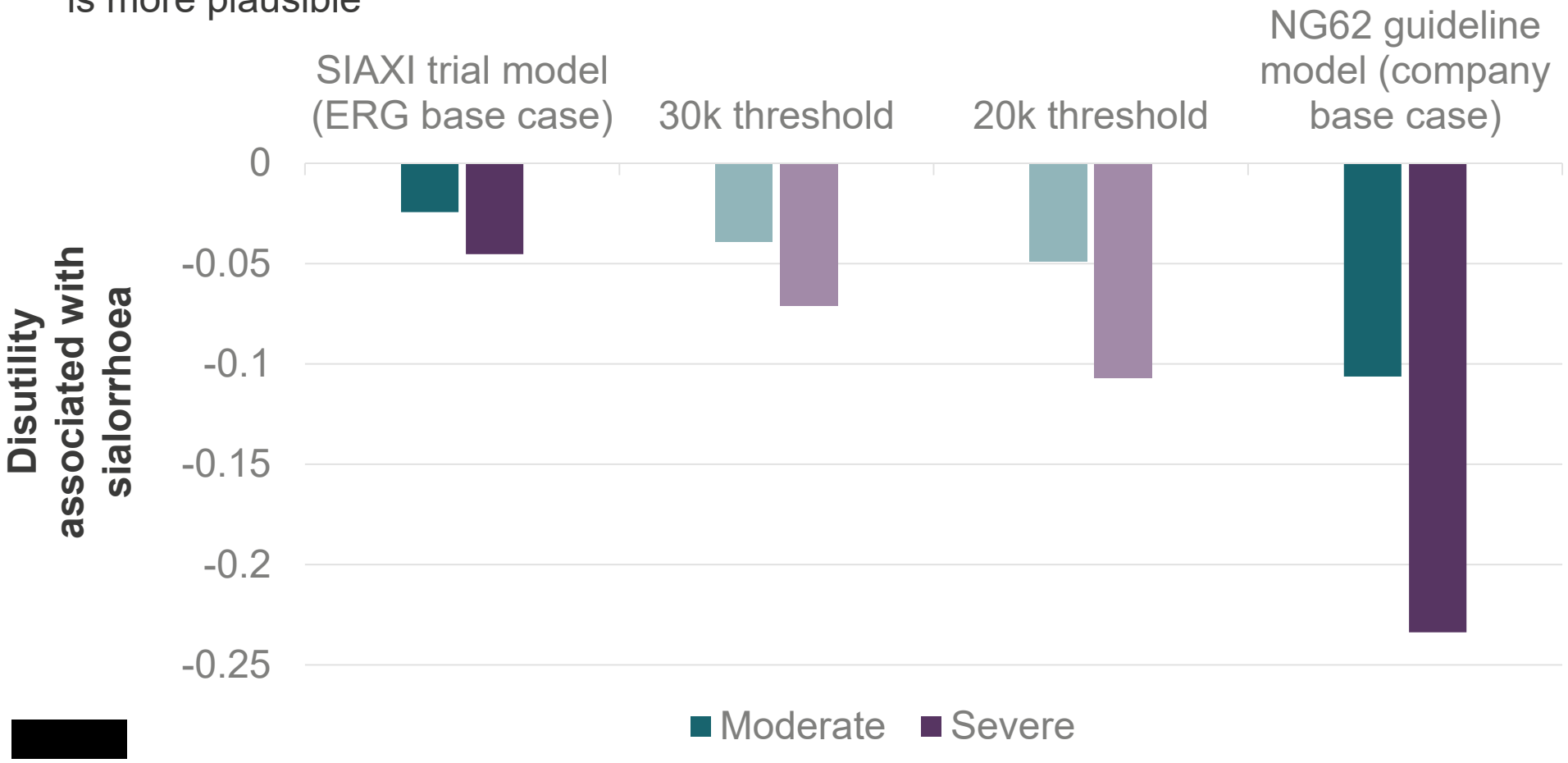
Final technical report judgement

- Technical team prefer EQ-5D-3L data and derived utility values because it is measured in a population that reflects the intended treatment population more closely
- Acknowledgement that there is substantial uncertainty because of the paucity of data
- With no survival benefit, the ICER is very sensitive to small changes in the utility values

[redacted]

Disutility threshold analysis - against SoC

- A threshold analysis was performed to provide the disutility values associated with sialorrhoea at a cost per QALY gained of £20k and £30k using the ERG base case assumptions
- Assumes a constant proportional relationship between sialorrhoea severity states
- Company: The “true” value likely lies between the two utility sets, but the NG62 guideline set is more plausible



[redacted]

Issue 4: Ultrasound guidance

Background

- Ultrasound imaging can be used to guide the injection site within salivary glands, or alternatively anatomical landmarks are used
- In the SIAXI trial, approximately 55% of injections used ultrasound guidance
- In the company economic model, this proportion are assumed to receive ultrasound guidance in NHS clinical practice
- ERG provided a scenario including cost of 100% of injections using ultrasound guidance

Company response

- Ultrasound guidance is used variably in UK clinical practice
- Changing costs of ultrasound guidance does not take into account improved efficacy from using ultrasound imaging

Association of British Neurologists comment

- Only a minority of cases would require ultrasound guidance

Final technical report judgement

- There is variability in the use of ultrasound guidance, so the company assumption of 55% is appropriate

[redacted]

What criteria are used to decide whether ultrasound guidance is used?

Issue 5: Implementation

Background

- Administration costs of CBTA may require additional NHS resources such as training and specialist centres

Company response

- CBTA is currently offered in specialist centres and this is unlikely to change
- Training would be necessary but would not be complex or onerous
- CBTA is currently administered by a wide variety of healthcare professionals so no significant additional resource would be required on an individual centre basis

Association of British Neurologists comments

- Some clinicians may need additional training
- CBTA treatment is currently provided in secondary and tertiary care

Final technical report judgement

- Clinicians would need additional training for administering CBTA injections
- It is unclear if this would have any implementation or cost implications

[redacted]

Issue 6: Resource use

Background

- No resource use data were collected within SIAXI
- Company assumes that improvements in sialorrhoea would reduced the number of speech and occupational therapy consultations required

Health state	Number of consultations per 16 weeks
Mild/no sialorrhoea (DSFS 2-3)	None
Moderate sialorrhoea (DSFS 4-6)	• 0.5 speech pathology • 0.5 occupational therapy
Severe sialorrhoea (DSFS 7-9)	• 1 speech pathology • 1 occupational therapy

- ERG provided a scenario exploring using the same resource use for mild, moderate and severe sialorrhoea (i.e. mild/no sialorrhoea costs for all patients)

Technical team judgement

- It is appropriate to model resource costs to be equivalent for people with severe and moderate sialorrhoea because the distinction is not clear in clinical practice

[redacted]

What frequency of resource use would be seen in clinical practice?

Additional areas of uncertainty

Issue	Cause of uncertainty
Efficacy of glycopyrronium bromide	Company assumes efficacy of glycopyrronium bromide is 75% of CBTA based on an assumption in NICE guideline for cerebral palsy in <25s due to lack of data on efficacy
Efficacy of anticholinergic treatments	Lack of data on other anticholinergic treatments so they are considered to have the same efficacy as glycopyrronium bromide
Adverse events	Lack of data on adverse events for glycopyrronium bromide means they were not modelled in the economic model, despite being a concern to patients and clinicians

[redacted]

Other issues for information

Issue	Cause of uncertainty
ERG utility regression model	The ERG provided an alternative utility regression model using the 3 sialorrhoea severity levels as explanatory variables rather than raw DSFS score and alternative covariate choice
Other ERG amendments	The ERG performed other minor corrections including correction of administration costs, assuming alternative discontinuation assumptions and modifying the continuity correction factor in the transition probability matrices. The technical team agreed with these changes and noted they had minimal effect on the ICER

Cost-effectiveness results (list price)

Intervention	Total costs (discounted)	Total QALYs (discounted)	Incr. costs	Incr. QALYs	ICER for CBTA* versus comparator (£/QALY)
Company base case (deterministic)					
CBTA plus Soc	£6,103	3.52	—		
Glycopyrronium bromide plus SoC	£14,966	3.34	-£8,863	0.18	CBTA plus SoC dominant
SoC alone	£3,010	3.20	£3,093	0.32	£9,583
ERG analyses – combined population (deterministic)					
CBTA plus Soc	£5,013	4.038	—		
Glycopyrronium bromide plus SoC	£9,730	4.008	-£4,717	0.029	CBTA plus SoC dominant
SoC alone	£2,594	3.987	£2,419	0.051	£47,309

*CBTA costs of Xeomin

[redacted]

Note: some values extracted from economic model, not in the committee papers

Scenario analyses (list price)

Scenario	Incr. costs	Incr. QALYs	ICER for CBTA + SoC versus SoC (£/QALY)
Company scenarios			
Company base case	£3,093	0.32	£9,583
Alternative anticholinergic comparator: Hyoscine hydrobromide	£1,498	0.18	£8,210
Alternative anticholinergic comparator: Atropine sulphate	£2,548	0.18	£13,964
Alternative mortality scenario (standardised mortality rate of 1.92 applied)	£2,977	0.31	£9,671
Assuming 1 consultation per 16 weeks for moderate/severe groups	£3,379	0.32	£10,470
ERG scenarios			
ERG analyses – combined population	£2,419	0.051	£47,309
ERG base case (probabilistic)	£2,390	0.053	£45,423
Assuming all patients require ultrasound scan	£2,652	0.051	£51,872
Assuming no additional resource use by sialorrhoea severity (0 visit per 16 weeks, all severity groups)	£3,053	0.051	£59,714

[redacted]

Note: some values extracted from economic model, not in the committee papers

Equality considerations

- Potential equality considerations raised by Parkinson's UK
  - **Age** Parkinson's disease predominantly impacts people aged over 65 years old
  - **Physical disabilities** Parkinson's disease is a movement related disorder, saliva management issues are due to change in posture and reduced lip seal
  - **Communication difficulties** Parkinson's disease can reduce the ability to communicate clearly
  - **Mental health problems** 31% of people with Parkinson's disease experience anxiety and 40% experience depression; these are often reported as the most distressing aspects of their condition

Innovation

- The company considers the drug to be innovative. However, the technical team considers that the relevant benefits associated with the innovation of the drug are adequately captured in the model

Social value judgement

- NICE expects advisory bodies to consider conditions that are associated with stigma as part of its social value judgements
- "Stigma may affect people's behaviour in a way that changes the effectiveness of an intervention and relief of stigma may not always be captured by routine quality of life assessments."

Is there a stigma associated with sialorrhoea?
If so, how should it be considered in this appraisal?

[redacted]

Key issues

- **Comparator and treatment choice**: [Issue 1]
  - Is glycopyrronium bromide an appropriate comparator for chronic sialorrhoea?
- **Health-related quality of life and utility values:** [Issue 3]
  - Can the EQ-5D-3L capture the health-related quality of life associated with sialorrhoea?
  - What are the appropriate utility values for sialorrhoea health states?
- **Ultrasound guidance**: [Issue 4]
  - What criteria are used to decide whether ultrasound guidance is used?
- **Resource use (speech, language and occupational therapy):** [Issue 6]
  - What frequency of resource use would be seen in clinical practice?
- **Social value judgement:**
  - Should stigma associated with sialorrhoea be considered in this appraisal?