Single Technology Appraisal

Glycopyrronium bromide cream for treating severe primary axillary hyperhidrosis [ID6487]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

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

1. **Company submission** from Leith Healthcare**:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Urgent clarification questions to company (sent ahead of regular clarification request)
   b. Clarification questions and company responses
   c. Follow-up response

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. British Association of Dermatologists
   b. Cornwall & IoS ICB

4. **External Assessment Report** prepared by BMJ TAG
   a. EAG report
   b. EAG report addendum

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

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Glycopyrronium bromide cream (Axhidrox®) for treating severe primary axillary hyperhidrosis [ID6487]

Company evidence submission

May 2025

File name	Version	Contains confidential information	Date
ID6487_GPB 1% cream_PAHH_Company-evidence-submission_v2.0_[REDACTED]	2.0	No	31 October 2025

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Abbreviations

A&G	Advice and guidance
ADR	Adverse drug reaction
AE	Adverse event
AHH	Axillary hyperhidrosis
AI	Activity impairment
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BDRM	Blind data review meeting
BL	Baseline
BMI	Body mass index
BMICE	Botulinum toxin > medication > iontophoresis > curettage > endoscopic thoracic sympathectomy
BNF	British National Formulary
BSA	Body surface area
BTX	Botulinum toxin
CCA	Cost comparison analysis
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CI	Confidence interval
CSR	Clinical study report
DLQI	Dermatology Life Quality Index
DRM	Data review meeting
EC	Exclusion criteria
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
EQ-5D	EuroQol- 5 Dimension
ETS	Endoscopic thoracic sympathectomy
EU	European Union
FAS	Full analysis set
FU	Follow-up
GBP	Great British Pound
GI	Gastrointestinal
GM	Gravimetric measurement
GP	General practitioners
GPB	Glycopyrronium bromide
HDSS	Hyperhidrosis Disease Severity Scale
HH	Hyperhidrosis
HidroQoL	Hyperhidrosis Quality of Life Index
HRG	Healthcare Resource Group
HRQoL	Health-related Quality of Life
HTA	Health Technology Assessment
IBMCE	Iontophoresis > botulinum toxin > medication > curettage > endoscopic thoracic sympathectomy
IC	Inclusion criterion
ICE	Iontophoresis > curettage > endoscopic thoracic sympathectomy
ICER	Incremental cost-effectiveness ratio
IMP	Investigational medicinal product
ITC	Indirect treatment comparisons
LYG	Life years gained
mAChR	Muscarinic acetylcholine receptors
MBICE	Medication > botulinum toxin > iontophoresis > curettage > endoscopic thoracic sympathectomy
MCID	Minimally clinically important difference
MedDRA	Medical dictionary for regulatory activities
Mg	Milligram
Min	Minute
ML	Millilitres
N	Number
NA	Non-applicable
NICE	National Institute for Health and Care Excellence
NHB	Net health benefits

NHS	National Health Service
NMA	Network meta-analysis
NMB	Net monetary benefits
ONS	Office for National Statistics
OR	Odds ratio
OWI	Overall work impairment
PAHH	Primary axillary hyperhidrosis
POC	Proof of concept
PPS	Per-protocol set
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROM	Patient-reported outcome measure
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q1	First quarter
QALY	Quality-adjusted Life Year
QoL	Quality of Life
QTc	Corrected QT interval
RCT	Randomised controlled trials
SAE	Serious adverse event
SAF	Safety analysis set
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single technology appraisal
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment emergent adverse event
U	Units
UK	United Kingdom
ULN	Upper limit of normal
US	United States
USD	United States Dollar
WKS	Weeks
WTP	Willingness-to-pay

1 Decision problem

This submission covers the full anticipated marketing authorisation for glycopyrronium bromide 1% cream (hereafter referred to as GPB 1% cream or Axhidrox®) as a treatment for adult patients with severe primary axillary hyperhidrosis (excessive underarm sweating).

The decision problem addressed within this submission aligns with the NICE final scope for this appraisal as described in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with severe primary axillary hyperhidrosis	Adults with severe primary axillary hyperhidrosis	Not applicable
Intervention	GPB 1% cream	GPB 1% cream	Not applicable
Comparator(s)	• Oral antimuscarinics such as propantheline bromide, off-label oxybutynin or off-label oral glycopyrronium bromide • Botulinum-toxin A (botox) injection	• Oral antimuscarinics such as propantheline bromide, off-label oxybutynin or off-label oral glycopyrronium bromide • Botulinum-toxin A (botox) injection	Not applicable
Outcomes	The outcome measures to be considered include: • disease severity • absolute change in sweat production • response rates • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • disease severity • absolute change in sweat production • response rates • adverse effects of treatment • health-related quality of life	Not applicable

Abbreviations: GPB, glycopyrronium bromide; NICE National Institute for Health and Care Excellence.

1.1 Description of the technology being evaluated

A description of GPB 1% cream is presented in Table 2. The United Kingdom (UK) smPC and public assessment report is not yet available. Details of the SPC from the European Decentralised Procedure are in Appendix A.

Table 2: Technology being evaluated

UK approved name and brand name	Axhidrox® (glycopyrronium bromide 1% cream)
Mechanism of action	Hyperhidrosis results from overstimulation of the eccrine sweat glands. Five muscarinic acetylcholine receptors (mAChR M1-M5) have been identified in the basolateral membrane of the sweat gland cells. As a competitive inhibitor of the mAChRs, glycopyrronium (GP) inhibits ACh-driven sympathetic actions on various exocrine glands, including sweat glands. In the sweat glands, this results in a reduction in sweat production and ultimately in reduced perspiration.
Marketing authorisation/CE mark status	GPB 1% cream is licensed for the topical treatment of severe PAHH in adults in 23 Member States of the European Economic area following completion of [redacted], with [redacted] acting as the reference member state. UK marketing authorisation is expected in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated UK marketing authorisation wording is, Axhidrox is indicated for the topical treatment of severe primary axillary hyperhidrosis in adults. GPB 1% cream is for topical use in the underarm area only and not for use in other body areas. The safety and efficacy of GPB 1% cream in children and adolescents aged 12–18 years has been shown in a clinical trial,[1] and is currently under review by authorities.

Method of administration and dosage	*Preparation of the pump before the first use* The multidose container requires priming before it is used for the first time. To get a full initial dose, the air trapped in the pump must be removed as follows: – Hold the pump at an angle (see illustration) and repeatedly press the pump down until cream comes out of the opening onto a piece of paper. – Slowly push the pump down fully another 10 times and put the pumped cream onto the paper. Dispose the paper with the dispensed cream via waste bin only. – The pump is now ready for use. Repeated preparation of the pump is not necessary for subsequent use.  *Regular application of the cream* After priming, the application of the cream is done using the cap as further detailed: – Hold the pump in one hand with the opening of the pump towards the removed cap of the pump (see illustration). – Fully press the pump twice to apply the recommended amount of cream to the top of the cap. – Using the cap, evenly distribute the cream in one armpit. – Repeat this process for the second armpit. – Afterwards, for safety, wash the cap and your hands immediately and thoroughly with soap and water. This is important to avoid contact of the cream with nose, eyes or mouth as well as with other persons – Tick off the number of treatments in the table on the outer carton 
Additional tests or investigations	No specific additional tests or investigations are associated with the administration of GBP 1% cream
List price and average cost of a course of treatment	Anticipated list price £[redacted] per tube An average of 5 tubes per patient per year results in annual cost per patient of £[redacted]
Patient access scheme (if applicable)	Not applicable. Leith anticipates that baseline commissioning for GPB 1% cream is a cost-effective use of NHS resources at the proposed list price.

Abbreviations: GPB, glycopyrronium bromide; mAChR, muscarinic acetylcholine receptor; NHS, national health service; PAHH, Primary Axillary Hyperhidrosis; UK, United Kingdom.

1.2 Health condition and position of the technology in the treatment pathway

1.2.1 Disease overview

Sweating is an important way to reduce the body's temperature, for example during strenuous physical activity or when exposed to a hot environment. Hyperhidrosis is a common skin condition characterized by abnormal levels of sweating beyond physiological need. Prevalence ranges from 1 to 5% worldwide, and it affects both sexes equally.[2,3] Prevalence of hyperhidrosis in the UK is unknown as it is underreported and underdiagnosed.[4]

Hyperhidrosis can be categorized as primary (idiopathic) or secondary to many other conditions[5] and can also be categorised by its location and whether it is focal or generalised. Primary hyperhidrosis often starts in childhood (palms and soles of feet) or at puberty (axillary).[3] The axillae (underarms) are the most commonly affected region in primary focal hyperhidrosis due to the large number of sweat glands in this area and sensitivity to both heat and stressful stimuli.[6] Other commonly affected focal locations of the body are palmoplantar (palms and soles of feet), craniofacial (scalp and face), and groin areas.[7]

The cause of primary hyperhidrosis is unknown, but is thought to be due to overreaction or hyperexcitability of the complex neurological pathways which control sweating. There is evidence of a hereditary predisposition for palmar hyperhidrosis; it is estimated that a child of a parent with the condition has a 1 in 4 chance of inheriting it.[8]

Hyperhidrosis is usually diagnosed when there is visible sweating, which interferes with daily activities, has lasted at least six months, and for which there is no known cause.[4]

Primary hyperhidrosis is a lifelong condition. A study of people with primary hyperhidrosis found that 88% had no improvement in symptoms or severity over time, which did not vary by age group.[9]

1.2.2 Impact of hyperhidrosis on patient quality of life

Hyperhidrosis can have a significant negative impact on patient´s' quality of life both socially and in the workplace and has been shown to have a greater impact on quality of life than other skin conditions such as atopic eczema, acne, psoriasis, or rosacea.[10]

A recent review of the literature on quality of life in hyperhidrosis found that patients have to cope with a range of impacts[11]

- **Psychological Impacts**: Patients with hyperhidrosis report a high level of psychological strain with an increased association of hyperhidrosis with anxiety and depression. In social situations, stress triggers sweat production, in turn, leading to higher stress levels. This cycle has an exponentially increasing negative effect on patients' quality of life.
- **Physical Impacts**: Excessive sweating affects activities of daily living such as wearing clothes, hygiene, and running errands. At least 40% of patients with hyperhidrosis report physical discomfort based on focus groups, interviews, and online survey data.
- **Social Impacts**: Hyperhidrosis has a significant negative impact on patients' social life and interactions. 75% of patients have reported impairment in social life, and emotional and mental health. Excessive sweating can result in embarrassment, anxiousness, sadness, anger, and feelings of hopelessness. Patients with hyperhidrosis may have difficulty in most aspects of social relationships such as physical contact, personal relationships, and intimacy. Patients report distress from a lack of being able to hide their symptoms and low self-esteem from worrying about other peoples' perceptions of them. They may exhibit avoidance behaviours, evading social situations, limited career opportunities, poor intimacy, or altered personal relationships because of their symptoms.
- **Medical Impacts:** Hyperhidrosis is associated with other comorbidities, which may contribute to worsening quality of life. Patients are found to have an increased risk of cutaneous disease with fungal (such as tinea pedis, candida, and onychomycosis), bacterial (especially pitted keratolysis), or viral infections (especially verruca). Excess sweat creates an environment suitable for skin barrier disruption, colonization, and infection.

The information on the impact on patient quality of life aligns with information Leith Healthcare received during from Q1 2025 market research calls with UK dermatologists who

frequently treat patients with hyperhidrosis (N=4).[12] The dermatologists remarked that hyperhidrosis affects every aspect of their patients' lives.

1.2.3 Impact of primary axillary hyperhidrosis (PAHH) on productivity

In a 2004 USA survey[2] of patients with primary axillary hyperhidrosis PAHH, one third of individuals reported that their sweating is barely tolerable and frequently interferes, or is intolerable and always interferes, with daily activities.

Recent attempts have been made to assess the level of negative impact of primary axillary hyperhidrosis PAHH on productivity.

A study from Japan[13] sought to calculate productivity loss, determined as absenteeism (%), presenteeism (%), and overall work impairment (OWI) (%) in working patients with axillary hyperhidrosis, and activity impairment (AI) (%) in full-time stay at home females with axillary hyperhidrosis. The monthly productivity loss per patient, corresponding to OWI (%), was £628. The monthly productivity loss per patient, corresponding to absenteeism (%) and presenteeism (%), was £10.50 and £617, respectively. The monthly productivity loss per patient, corresponding to AI (%), was £918.

Hyperhidrosis clearly has an impact on patients' ability to carry out daily tasks, impacting productivity and creating significant practical ongoing difficulties for patients with the condition.

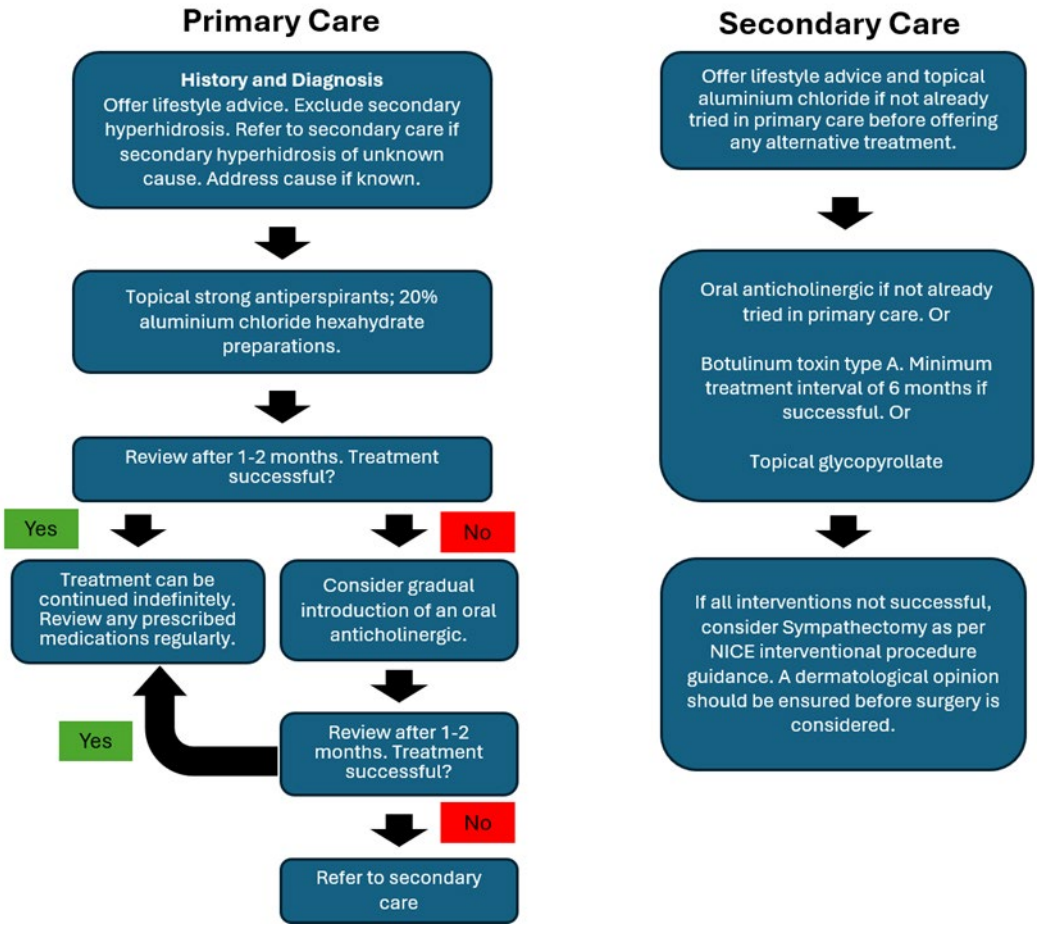
1.2.4 Current care pathway and unmet medical needs

The main goals of hyperhidrosis treatment are to improve the quality of life for the affected individual and reduce excessive sweating. A wide range of interventions are available for hyperhidrosis,[4] however there remain significant unmet needs for patients. There is no NICE guideline on hyperhidrosis and only licensed medicines for the second line management of hyperhidrosis are botulinum toxin a (BTX)[14] and propantheline bromide.[15]

A significant barrier to treating hyperhidrosis is the lack of patients seeking out medical care. A survey of 1,958 patients revealed that 48.9% of patients sought treatment after 10 or more years after the onset of hyperhidrosis.[16] Data from the UK indicated that only half of patients with hyperhidrosis ever discuss their condition with a healthcare professional.[17] When patients do seek medical help, it can be hampered by poor clinical guidelines, a lack of scientific evidence for the treatments being offered, and variation in the availability of treatment depending on location.[17,18]

Referrals to secondary care for HH are subject to increasingly long wait times, some areas have removed treatment with BTX completely, in some areas GPs won't attempt treatment with oral anticholinergics without referral to secondary care. Secondary care dermatologists in some areas are supporting primary care colleagues to manage patients with HH in primary care through Advice and Guidance.[12]

Figure 1: Current care pathway for PAHH



Abbreviations: NICE, National Institute for Health and Care Excellence; PAHH, Primary Axillary Hyperhidrosis.

Initial management of hyperhidrosis is provision of lifestyle advice and use of strong aluminium salt antiperspirants.[4] If relief from hyperhidrosis is insufficient, second line treatments are warranted. A 2017 systematic review of interventions for hyperhidrosis in secondary care[18] stated that the evidence for the effectiveness and safety of second-line treatments of primary hyperhidrosis is limited overall. Most studies were small, rated as being at high risk of bias and poorly reported. There was insufficient evidence to draw firm conclusions regarding the relative effectiveness and safety of any active second-line treatments. This review was not specific to PAHH so the scope was broader than the patient population relevant to GPB 1% cream. Regarding the treatments relevant as comparators in this assessment the review stated.

- There is moderate-quality evidence of a large effect of subcutaneous BTX on symptoms of axillary hyperhidrosis in the short and medium term (up to 16 weeks), and of a small to moderate positive effect on quality of life in the short term (up to 4 weeks), compared with placebo.[18] BTX may be associated with higher patient satisfaction in the short to medium term, as well as a higher incidence of adverse events, notably injection site pain and compensatory sweating.

- There is low-quality evidence[18] suggesting a short-term small benefit of oral oxybutynin in reducing hyperhidrosis symptoms and a short-term improvement in quality of life compared with placebo, although there is insufficient evidence to determine whether or not the effectiveness of oxybutynin differs according to target area. There is low-quality evidence that, compared with placebo, oral methantheline bromide has a short-term positive effect on axillary hyperhidrosis symptoms and quality of life, although this effect is small and may not be clinically significant. There is evidence suggesting that both oxybutynin and methantheline bromide are associated with a high incidence of dry mouth symptoms. There were no studies assessing the clinical effectiveness of propantheline bromide for hyperhidrosis. [methantheline bromide is not available in England and Wales].

Leith Healthcare's market research[12] and documented UK experience[16] demonstrates that oral anticholinergics are not typically a long-term option for the management of axillary hyperhidrosis due the side effects many patients experience.

Patients are often advised to use oral medications only when necessary (e.g. when going to public events), rather than on a daily basis. It is recognised that there is variation in how well patients may tolerate one anticholinergic over another, however in some areas, the use of oral anticholinergics in primary care does not take place (which is in accordance with the NICE Clinical Knowledge Summary)[4] and in some areas primary care can only use propantheline bromide because it is the only licensed option. Patients may not able to try another oral anticholinergic until after referral to secondary care.[12] There are also increasing concerns about the long-term use of oxybutynin and cognitive impairment,[17] that may limit the willingness of healthcare professionals to initiate treatment for the long term.

BTX is acknowledged as a suitable option for the second line management of axillary hyperhidrosis[12,18] however access to BTX through the NHS has been variable for many years and has become even more restricted since the emergence from the response to Covid-19[12,19] as pressure on dermatology services and consultant time has increased. Even where BTX is available through the NHS, there can be access restrictions based on self-funded treatments that must have been tried prior to referral[20], on the total number of administrations that will be provided to a patient through the NHS,[19] or on the frequency with which re-administration can occur.[21] As a result, BTX is mainly available privately and typically costs £400-£600 per administration. Given that a typical patient will need more than 1 administration per year, this cost can be beyond the means of many patients.

The British Association of Dermatologists list glycopyrrolate (glycopyrronium) 2% w/w in cetomacrogol cream as a special order (unlicensed) product recommended for use to treat disabling facial hyperhidrosis.[22] Clinical expert opinion[12] suggests that this is occasionally provided to patients for axillary hyperhidrosis but only in a limited number of centres because of the unlicensed status, difficulty accessing outside of supply from hospital pharmacy, and the cost (£129.70 for 30g in April 2025 Drug tariff).[23]

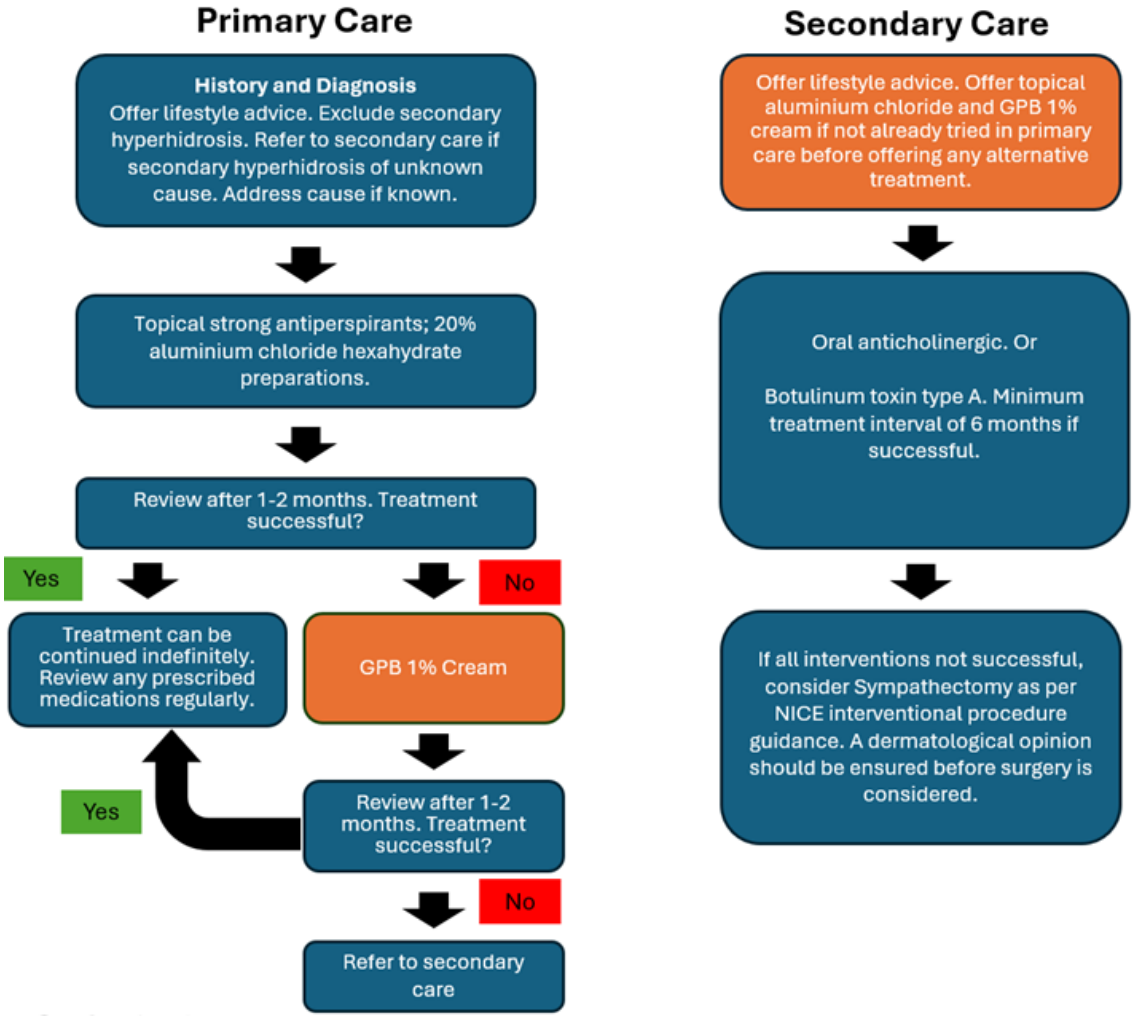
1.2.5 Unmet need

For patients with severe PAHH that has failed to adequately respond to first line therapy, there is an unmet need for a licensed, evidence-based, effective, and accessible treatment that places minimal burden on NHS resources.

GPB 1% cream would be positioned in the treatment pathway as an option for use in primary care for patients with severe PAHH, prior to their referral to secondary care. Where referral to secondary care had taken place and GPB 1% cream had not been trialled, it would be an option for initiation in secondary care before trying alternative treatments.

The proposed place in therapy for GPB 1% cream is shown in Figure 2 below.

Figure 2: Proposed care pathway for PAHH with GPB 1% cream



Abbreviations: GPB, glycopyrronium bromide; NICE, National Institute for Health and Care Excellence; PAHH, Primary Axillary Hyperhidrosis.

1.3 Equality considerations

The following potential equality issues were raised at scoping consultation stage:

- The population considered in the scope is adults, however HH often starts during childhood and adolescence, and causes considerable disruption of both social life and education. Treatment of adolescents with HH could make a significant impact on their lives. A clinical study of GPB 1% cream in children 12 and older is complete[1] and [redacted]
- Hyperhidrosis is often self-managed – there are significant out of pocket costs which may lead to inequality based on income and affordability. Patients may need to purchase absorbent clothing, spend more on clothing changes and cleaning products, and potentially self-fund BTX treatment due to lack of availability through the NHS[21].

There are challenges regarding geographic availability for some current therapies – for example BTX, which is available in some areas but not others. Where BTX is available there can be restrictions on the number of treatments allowed per year or the total number of treatments provided by the NHS.[21,22]

2 Clinical effectiveness

2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted in March and April 2025 to identify evidence of clinical effectiveness for GPB 1% cream and established treatments in severe primary axillary hyperhidrosis. Full details of the methodology and results of the clinical SLR are provided in Appendix B.

The SLR identified two publications describing a pivotal Phase 3a/3b study, which included a 4-week placebo-controlled period,[24] followed by a 72-week open label extension.[25] These studies provide evidence on the efficacy and safety of Axhidrox for the treatment of severe PAHH in adults aged18 years or older. Table 3 outlines the details of the Phase 3a/3b study and the related, unpublished Phase 1b study (NCT03037788).

For comparator studies, the SLR identified 53 publications on botulinum toxin and eight on oxybutynin. Of these, one RCT for oxybutynin[26] and one RCT for botulinum toxin A[27] for the treatment of severe AHH in adults aged 18 years or older were considered relevant for the submission, as both reported a change in HDSS score as an outcome and included populations comparable to the UK. Further details of these studies, the other studies identified in the SLR, and the rationale for selection of studies included in the indirect treatment comparison are provided in Section 2.9.

2.2 List of relevant clinical effectiveness evidence

Table 3: Clinical effectiveness evidence

Study	**Hyp1-18/2016 Phase 3a part[24]**	**Hyp1-18/2016 Phase 3b part[25]**	**Hyp-02/2015 Phase 1b[28]**
Study design	Prospective, randomized, double-blind, placebo controlled, multicentre, Phase IIIa, parallel group	Long-term, open label, single-arm, multicentre, Phase IIIb,	Single centre, randomised, placebo-controlled, double-blind, dose finding study
Population	Adults (18-65 years) with severe PAHH defined by gravimetry (> 50 mg/5 min axillary sweating) and HDSS 3-4	Adults (18-65 years) with severe PAHH defined by gravimetry (> 50 mg/5 min axillary sweating) and HDSS 3-4	Adults (18-65 years) with severe PAHH defined by gravimetry (> 50 mg/5 min axillary sweating in women and 100 mg/5 min in men) and HDSS 2-4
Intervention(s)	Once daily treatment with GPB 1% cream at recommended dose (4,4 mg GP per axilla) for 4 weeks.	For newly recruited patients: Once daily treatment with GPB 1% cream at recommended dose (4,4 mg GP per axilla) for the first 4 weeks. From 5th week on the application frequency at recommended dose (4,4 mg GP per axillary) was reduced to at least twice per week depending on individual needs. For roll-over patients from Phase 3a part: From 5th week on the application frequency at recommended dose (4,4 mg GP per axilla) was reduced to at least twice per week depending on individual needs.	Once daily treatment for 14 days with 0.5 % GPB cream, 1.0 % GPB cream or 2.0 % GPB cream

Comparator(s)	Placebo	None	Placebo
Indicate if study supports application for marketing authorisation	Yes	Yes	Yes
Indicate if study used in the economic model	Yes	Yes	No
Rationale if study not used in model	Not applicable	Not applicable	Too short duration and very low patient numbers
Reported outcomes specified in the decision problem	Primary endpoint ▪ Absolute change in sweat production assessed by gravimetry from Baseline to Day 29 in the 1% GPB group compared with the placebo group. Key secondary endpoints ▪ The percent of responders assessed by the HDSS scale (≥2-point improvement from baseline) ▪ The absolute change in the HidroQoL from baseline to Day 29 in the GPB 1% group	Primary endpoint - (newly recruited patients only) ▪ Absolute change in total sweat production assessed by gravimetry from Baseline to Week 12. Key secondary endpoints ▪ Percentage of responders assessed by the HDSS (≥2-point improvement from Baseline) at Week 12 (greater than 25%) ▪ Percentage of responders assessed by the HDSS (≥2-point improvement from	Efficacy assessments included gravimetry of sweat production (performed pre-dose, and at Day 2, 3, 4, 8, 14 and 21), assessment of the HDSS) (performed predose, and at Day 2, 3, 4, 5, 6, 8, 14 and 21), and the QoL questionnaires (DLQI) and HidroQoL performed pre-dose, and at Day 8, 14 and 21.

	compared with the placebo group. ▪ Frequency, severity and relation of adverse events (AEs), SAEs, TEAEs, suspected unexpected serious adverse reactions (SUSARs), and discontinuations due to AEs;	Baseline) at Week 28 (greater than 25%) ▪ Absolute change in the HidroQoL from Baseline to Week 12. ▪ Frequency, severity, and relation of AEs, SAEs, TEAEs, SUSARs, and discontinuations due to AEs;
All other reported outcomes	▪ DLQI questionnaire ▪ Local tolerability at the application site assessed by the investigator using a skin reaction score; ▪ Vital signs (heart rate, blood pressure, and body temperature); ▪ 12-lead ECG assessments; ▪ Neurological examination; ▪ Safety laboratory (haematology, chemistry, and urinalysis).	Up to and including Week 12 ▪ DLQI questionnaire ▪ Local tolerability at the application site assessed by the investigator using a skin reaction score; ▪ Neurological examination; ▪ Safety laboratory (haematology, chemistry, and urinalysis); ▪ Product use per month. Week 13 to Week 72 ▪ DLQI questionnaire ▪ Local tolerability at the application site assessed

		by the investigator using a skin reaction score; ▪ Vital signs (heart rate, blood pressure, and body temperature; only assessed at Week 28 and Week 72); ▪ 12-lead ECG (only assessed at Week 72); ▪ Neurological examination (only assessed at Week 72); ▪ Safety laboratory (haematology, chemistry, and urinalysis; only assessed at Week 72); ▪ Product use per month

Abbreviations: AEs, adverse events; DLQI, dermatology life quality index; ECG, electrocardiogram; GP, glycopyrronium; GPB, glycopyrronium bromide; HDSS, hyperhidrosis disease severity scale; HidroQol, hyperhidrosis quality of life index; min, minute; mg, milligram; PAHH, primary axillary hyperhidrosis; QoL, quality of life; SAES, serious adverse events; SUSARs, serious unexpected adverse reactions; TEAEs, treatment emergent adverse events.

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Clinical trial programme objectives

The objectives of the Phase 3 clinical trial programme were to assess the efficacy and safety of GPB 1% cream compared to placebo and assess the long-term efficacy and safety of GPB 1% cream in patients with severe PAHH.

Efficacy endpoints included measures of absolute sweat reduction, obtained by central laboratory recorded gravimetric measurements (measurement of sweat weight), and patient reported improvement measured by three quality of life instruments.

Given hyperhidrosis is typically a lifelong condition, the clinical trial programme sought to establish that treatment with GPB 1% cream, with reduced application frequency after the initial four-week treatment period, continued to demonstrate, efficacy, tolerability and improvement in patient quality of life over a 72-week period.

2.3.2 Overview of Hyp1-18/2016 Phase 3a and Hyp1-18/2016 Phase 3b

The pivotal study for GPB 1% cream was a randomised, double-blind, dose-confirming, parallel-group design study to assess the efficacy and safety of topical 4-week treatment with GPB 1% cream versus placebo cream (vehicle cream without active ingredient) in a Phase 3a part[24] followed by an open-label Phase 3b part[25] to assess the long-term efficacy and safety of GPB 1% cream in patients with severe PAHH. The study was conducted at 37 centres in Germany, Poland, Hungary, United Kingdom (UK), Denmark, and Sweden. The Phase 3a part was conducted at 21 centres, with no centres in Poland.

In the dose-confirming Phase 3a part,[24] 171 patients were randomized in a 1:1 ratio to once-daily treatment with GPB 1% cream (87 patients) or placebo cream (84 patients) for 4 weeks (Figure 3). During the double-blind treatment, the safety and efficacy were assessed 14 and 28 days after the first administration of the investigational medicinal product (IMP; at Day 15 and Day 29/end of treatment [EOT]a).

At the EOTa visit of the Phase 3a part,[24] all patients were offered to continue open-label treatment with GPB 1% cream (Phase 3b part), irrespective of the treatment applied during the Phase 3a part. Of the 166 patients who completed the Phase 3a part, 161 patients continued in the 3b part of the study. For these patients, Day 29/EOTa corresponded to Week 4 of the Phase 3b part.[25]

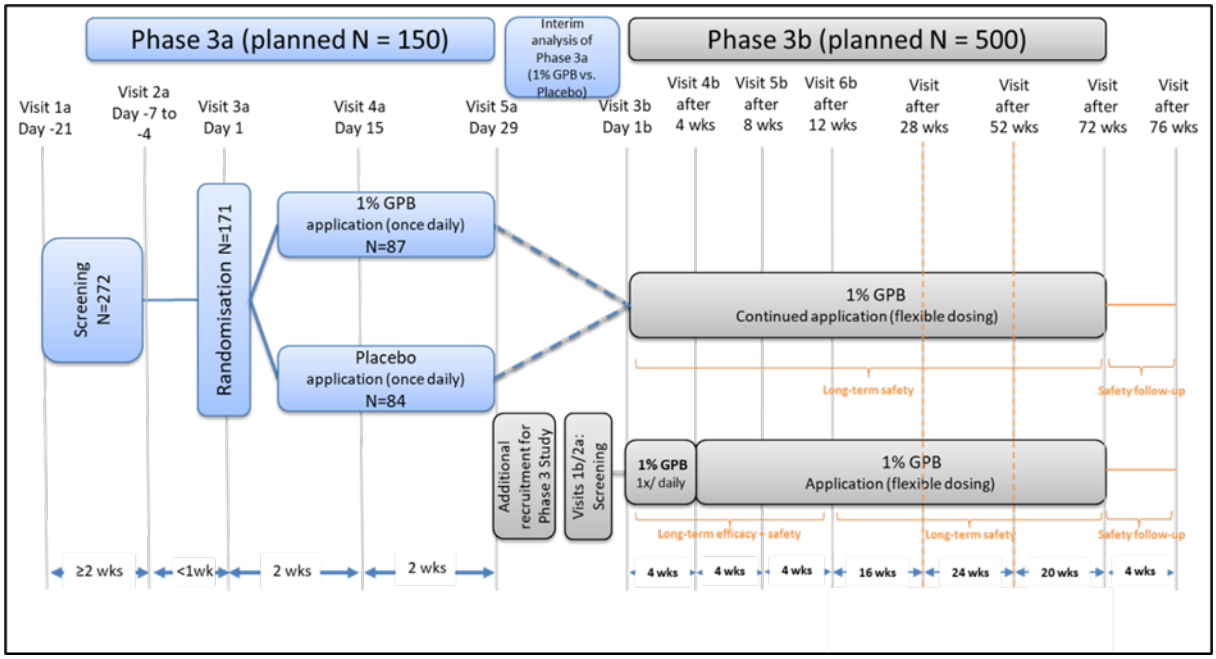
To achieve the planned total of 500 patients for the long-term 3b part of the study (including roll-over patients from Phase 3a part), 566 additional patients were screened and 357 patients included, who are in the following referred to as ‘newly recruited patients’, where applicable.[25]

During the Phase 3b part,[25] patients were treated with GPB 1% cream for up to 72 weeks. Newly recruited patients applied GPB 1% cream once daily for the first 4 weeks (analogous to the treatment applied during Phase 3a part). After the first 4 weeks of treatment (ie, after

completion of Week 4), all patients (including those who rolled over from the Phase 3a part) could apply GPB 1% cream as needed (at least twice per week but at most once daily) up to Week 72/EOTb), followed by a 4-week safety follow-up. The efficacy of treatment with GPB 1% cream was assessed for the primary and most key secondary endpoints at Week 12 (with additional efficacy assessments during the remaining treatment period, until Week 72), while the long-term safety was assessed up until Week 76.

A 4-week treatment period was chosen for the double-blind Phase 3a part to avoid an unreasonable burden for patients assigned to placebo treatment during a longer treatment period. Patients included in this study were not allowed to use any deodorants or antiperspirants during the study, which may have caused a high level of psychological suffering due to the underlying condition.

Figure 3: Flow chart of the study design for Hyp1-18/2016



Source: Hyp-18/2016 Phase3a/b CSR[29]
Abbreviations: GPB, glycopyrronium bromide; wks, weeks.

2.3.2.1 Prior and concomitant therapy

Investigators were provided with a list of medications that may induce sweat production. The use of these medications was prohibited from Day -21 to the end of the study.[29] Antiperspirants with ≥20% aluminium-containing compounds were prohibited from Screening Visit1a/b onward. Antiperspirants with <20% aluminium-containing compounds cholinomimetic and anticholinergic treatment, muscle relaxants and drugs that may have muscle-relaxant action, and oral herbal medicine and topical treatments for hyperhidrosis were prohibited from 1 week before the GM Screening (Visit 2a) until Week 72. The use of deodorants (without aluminium) was not permitted from 1 week before the GM Screening until the end of the once-daily treatment period at Day 29/Week 4. Thereafter, the use of aluminium-free deodorants was permitted. The use of antibiotics was prohibited from the first

IMP administration until the end of the once-daily treatment period at Day 29/Week 4. Using topically applied antibiotics was permitted.[29]

Oral contraception was only permitted, if the treatment had already started at least 3 months (i.e. 3 monthly cycles) before the first application and patients agreed to maintain treatment throughout the study period and until 1 cycle after the last dose.[29]

The use of antidepressants was only permitted if the patient had been on stable medication for at least 3 months before Screening and agreed to maintain product and dose throughout the study.[29]

Generally, patients had to maintain their standard therapies during the study. In consultation with the sponsor, patients could be withdrawn from the study if other concomitant medications were required or were taken without previous consultation.[29]

2.3.2.2 Inclusion and exclusion criteria

***Requirements for inclusion were*:**[24]

- Diagnosis of severe primary axillary hyperhidrosis with a HDSS score of 3 or 4;
- At least 50 mg of sweat production in each axilla measured gravimetrically at room temperature and at a humidity consistent with the normal climate in that area over a period of 5 minutes (patients should have acclimatized to that room for at least 30 minutes);
- Men and women aged 18 to 65 years at the time of informed consent with a body mass index (BMI) of 18-32 kg/m^2;
- Corrected QT (QTc) ≤450 msec, or QTc <480 msec in patients with bundle branch block;
- Female patients of childbearing potential had to have a negative pregnancy test at Screening;
- Female patients of childbearing potential had to use (for a least 3 monthly cycles before the first dose, during the study, and 1 cycle after the last dose of the IMP) a highly effective method of contraception or birth control (failure rate less than 1% per year when used consistently and correctly) and should have been informed of the potential risks associated with becoming pregnant while enrolled in this clinical investigation. Reliable methods for this study were: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, sexual abstinence or vasectomized sexual partner. *Abstinence was only accepted as true abstinence when this was in line with the preferred and usual lifestyle of the patient (periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods and withdrawal] was not an acceptable method of contraception).* Postmenopausal (no menses for at least 1 year without alternative medical cause) or surgically sterile female patients (tubal ligation, hysterectomy or bilateral oophorectomy) could be enrolled.

- Able to comply with protocol requirements, including blood sample collection;
- The patient was capable of understanding the nature, significance and implications of the clinical trial and to form a rational intention in the light of the facts, voluntarily agreed to participation and the study's provisions and had duly signed the informed consent form;
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <2 x upper limit of normal (ULN), alkaline phosphatase and bilirubin ≤1.5 x ULN at Screening (free bilirubin
- ≥1.5 × ULN will not directly lead to study discontinuation if bilirubin fraction test result of direct bilirubin <35% is available).

Patients with any of the following were to be excluded from study participation:[24]

- Known allergy to any of the components in the investigational product;
- Hypersensitivity against glycopyrrolate;
- Secondary hyperhidrosis, e.g., hyperhidrosis that was secondary to other underlying diseases including hyperthyroidism, lymphoma, malaria and climacteric hyperhidrosis;
- Previous surgical treatment of hyperhidrosis including sympathectomy, surgical debulking of the sweat glands, subcutaneous tissue curettage and ultrasonic surgery;
- Botulinum toxin treatment for the treatment of axillary hyperhidrosis in the previous 4 months;
- Presence or history of neuromuscular disease;
- Angle closure glaucoma or its precipitation (narrow angle);
- Mycotic, other skin infections and other dermal disorder including infection at anticipated application sites in either axilla;
- Significant cardiovascular disease, thyrotoxicosis and men with a history of urinary retention requiring catheterization due to prostatic hypertrophy or severe obstructive symptoms of prostatic hypertrophy;
- Significant cardiac arrhythmia such as tachycardiac atrial fibrillation and very frequent extrasystoles;
- Patients with uncontrolled diabetes mellitus;
- Patients with severe renal impairment *(including Gilbert's syndrome)*;
- Patients with active or clinical history of asthma *(within the last 10 years)* or chronic bronchitis;
- Patients with *a history of* ileus, gastrointestinal stenosis, pronounced chronic inflammatory bowel disease, toxic megacolon;
- Patients with epilepsy;

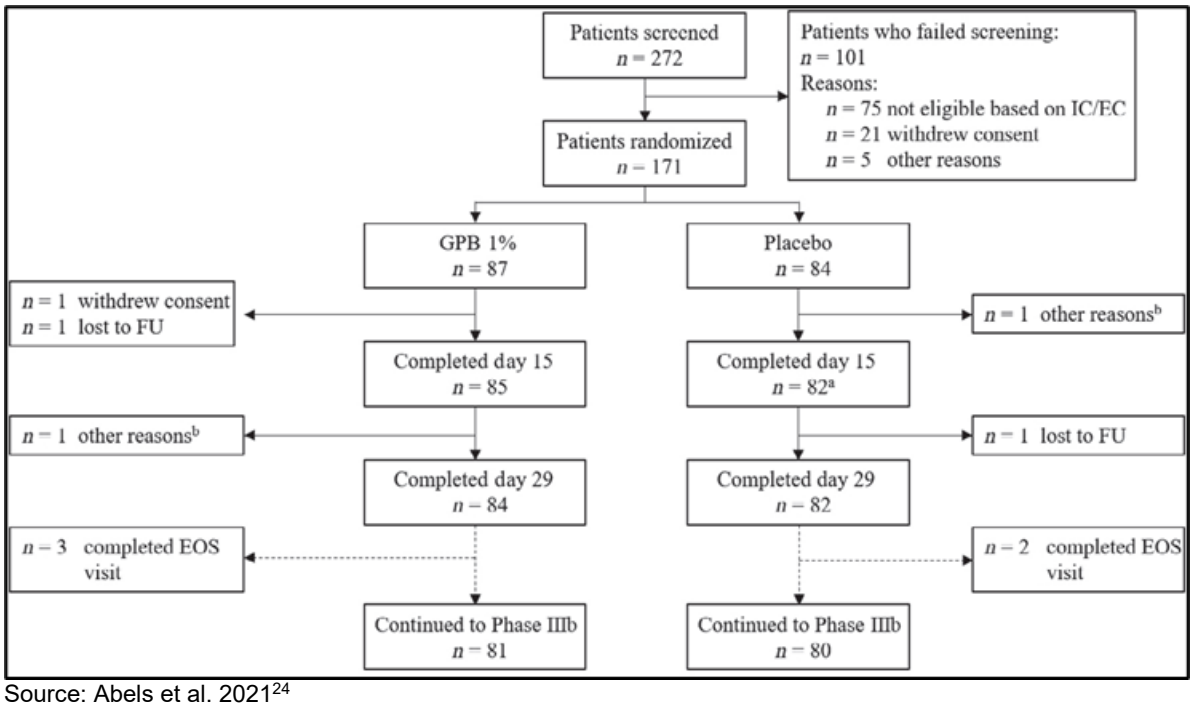
- Women who were pregnant, lactating, possibly pregnant or planning a pregnancy during the study period;

Use of prohibited medication or treatment:[24]

- Use of investigational drugs within 30 days or 5 half-lives (whichever was longer) or participation in another clinical trial within 30 days prior to the planned first dosing;
- Psychiatry disorder or cognitive disorder that may have affected the patient's ability to give informed consent or to follow specified study procedures;
- Positive serology test for hepatitis B or C virus, or human immunodeficiency virus 1 or 2;
- History of alcohol or drug abuse within the last 3 years;
- Any condition or situation that, in the investigator's or sub-investigator's opinion, may have interfered with the patient's participation in the study;
- Employees of the sponsor or sponsor's representative; employees or relatives of the investigator;
- Patients who were detained officially or legally to an official institute or those that had been committed to an institution by an order issued either by the judicial or the administrative authorities;
- Any score higher than 1 (i.e. 2 or 3) in the neurological examination;
- Patients with myasthenia gravis;
- Patients under treatment with potassium chloride;
- Patients with a disturbed blood-brain-barrier (such as patients with recent [within 1 year of Screening] craniocerebral trauma, chemotherapy, radiation therapy, skull opening surgeries, or intravenous drug users);
- Patients with psoriasis inversa or psoriasis pustulosa generalisata.

2.3.2.3 Hyp1-18/2016 Phase 3a | Patient disposition and study procedure

Figure 4: Phase 3a patient disposition



Source: Abels et al. 2021[24]
Notes: [a]1 patient missed the Day 15 visit but returned for Day 29; [b] 'Other reasons' was specified as 'no or not enough effect of the treatment'
Abbreviations: IC, inclusion criteria; EC, exclusion criteria; EOS, end of study; FU, follow-up; GPB, glycopyrronium bromide; N, number of patients.

The initial screening visit was followed by a washout phase of 2 weeks. Safety and efficacy were assessed on days 15 and 29. Use of a dispenser ensured the exact dosing of 0.54 g GPB 1% cream to each axilla per day. At the end of the study period dispensers were returned and weighed. As a special precaution, no shaving/depilation of armpits was allowed 14 days before the study or during it; trimming to 1 cm was permitted.[24]

Measurements

Gravimetric measurements (screening, baseline and day 29).

Gravimetric measurements were conducted at room temperature and at a humidity consistent with the normal local climate. After an acclimatization period of at least 30 min, axillary hair was trimmed, and axillae were dried with an absorbent paper towel. Standardised filter paper was placed on both axillae for 5 min. Weighing of the standardised filter paper before and after the gravimetric measurements was performed in a central laboratory.[24]

Hyperhidrosis Disease Severity Scale (HDSS)

The HDSS is a disease-specific diagnostic tool that provides a qualitative measure of the severity of the patient's condition based on how it affects daily activities. Each of four possible answers is assigned a value on a 4-point scale ranging from 1 to 4.[24]

Hyperhidrosis Quality of Life Index (HidroQoL©)

HidroQoL is a validated patient-reported outcome measure (PROM) used to capture the Quallity of life (QoL) of patients with HH. Two domains – daily life activity and psychosocial life – are assessed, with 6 and 12 questions, respectively. Questions are rated on a 3- point scale and a summary score for each domain and overall score is calculated. In 2020, the HidroQoL was revalidated specifically for PAHH and the minimally clinically important difference (MCID) for treatment response has been defined as an improvement of ≥ 4 points.[24]

Dermatology Life Quality Index (DLQI)

The DLQI is a validated questionnaire used to measure the impact of skin disease on the quality of life of the affected person. It consists of 10 questions that are answered on a 4-point scale from 0 to 3.[24]

Safety and tolerability

The frequency and severity of adverse events (AEs), serious AEs (SAEs) and treatment-emergent AEs (TEAEs) were recorded. Using a skin reaction score, local tolerability at the application site was assessed by the investigator.[24]

Endpoints

The primary endpoint was defined as the absolute change in sweat production with the GPB 1% cream vs. placebo from baseline to day 29, as assessed by gravimetry. Key secondary endpoints were the comparison between GPB 1% cream and placebo regarding absolute change in HidroQoL score from baseline to day 29 and the percentage of responders based on HDSS score at day 29 (improvement of ≥ 2 points).[24]

Table 4: Patient demography and baseline characteristics (FASa)

Demography		GPB 1% cream (N = 87)	Placebo (N = 84)	Total (N = 171)
Sex, N (%)[a]	Male	44 (50.6)	43 (51.2)	87 (50.9)
	Female	43 (49.4)	41 (48.8)	84 (49.1)
Race, N (%)[a]	White	86 (98.9)	81 (96.4)	167 (97.7)
	Black	1 (1.1)	-	1 (0.6)
	Asian	-	2 (2.4)	2 (1.2)
	Other	-	1 (1.2)	1 (0.6)

Baseline characteristics			
Age [years], median (range)	36.0 (18-65)	36.0 (18-65)	36.0 (18-65)
Body height [cm], median (range)	175.00 (155.0-198.0)	173.00 (153.0-196.0)	173.00 (153.0-198.0)
Body weight [kg], median (range)	76.40 (49.0-114.3)	76.10 (50.0-117.8)	76.40 (49.0-117.8)
sBMI [kg/m²], median (range)	25.50 (18.4-32.0)	25.05 (19.5-32.0)	25.10 (18.4-32.0)
BSA [m²], median (range)	1.94 (1.5-2.4)	1.90 (1.5-2.5)	1.93 (1.5-2.5)
Sweat production [mg], median (range)[b]	227.60 (0.2 - 1180.9)	252.25 (11.0 - 1012.8)	NA

N = 0 is shown as '-'.

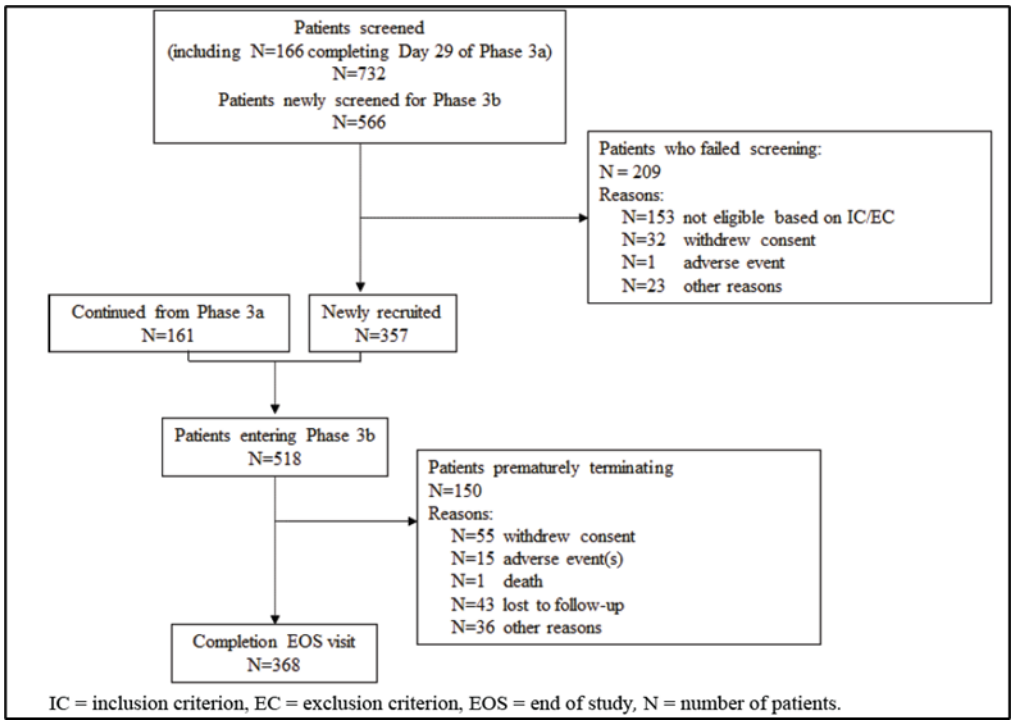
Source: Hyp-18/2016 Phase3a/b CSR [29]

A Percentages are based on the number of patients in the treatment group. B At Baseline, values below 50 mg were allowed.

Abbreviations: BMI, body mass index; BSA, body surface area; FASa, full analysis set (Phase 3a); GPB, glycopyrronium bromide; N, number of patients; NA, not applicable.

2.3.2.4 Hyp1-18/2016 Phase 3b | Patient disposition and study procedure

Figure 5: Hyp1-18/2016 Phase 3b patient disposition



Source: Szeimies et al. 2022[25]

Abbreviations: EC, exclusion criterion; EOS, end of study; IC, inclusion criterion; N, number of patients.

The initial screening visit was followed by a washout phase of 2 weeks. Sweat production was measured by gravimetric measurements at baseline, weeks 4 and 12. Patients reported

outcomes, safety and efficacy outcomes were assessed throughout the study at weeks 4, 8, 12, 28, 52 and 72.[25]

Measurements

The same measurements were performed as in the phase 3a part (Section **Error! Reference source not found.**).[24]

Endpoints

The primary endpoint was defined as the absolute change in sweat production from baseline to week 12. Key secondary endpoints were the percentage of responders with a ≥2-point improvement from baseline at weeks 12 and 28, as assessed by HDSS, and the absolute change in HidroQoL score from baseline to week 12. Further secondary endpoints were assessed, such as: Absolute change in the HDSS, HidroQoL and DLQI from baseline to weeks 4, 8, 12, 28, 52 and 72 (if not already assessed as a key secondary endpoint).[25]

Table 5: Hyp1-18/2016 Phase 3b: Patient demography and baseline characteristics (FASb, FASnewb)

Demography		**FASb (N = 518)**		**FASnewb (N = 357)**	
Sex, N (%)[a]	Male	244	(47.1)	160	(44.8)
	Female	274	(52.9)	197	(55.2)
Race, N (%)[a]	White	494	(95.4)	337	(94.4)
	Black	4	(0.8)	3	(0.8)
	Asian	8	(1.5)	6	(1.7)
	Other	12	(2.3)	11	(3.1)
Baseline characteristics					
Age [years], median (range)		33.0	(18 - 65)	32.0	(18 - 65)
BMI [kg/m²], median (range)		25.25	(18.1 - 32.3)	25.40	(18.1 - 32.3)
BSA [m²], median (range)		1.91	(1.28 - 2.60)	1.91	(1.28 - 2.60)
Sweat production [mg], median (range)[b]		NA		212.40	(0.2 - 1667.1)[c]

Source: Hyp-18/2016 Phase3a/b CSR [29]

Notes: aPercentages are based on the number of patients in each analysis set. [b]Assessed for newly recruited patients only. Missing baseline values were replaced with values from the GM assessments at Screening 2b.

[c]The sweat production at Baseline was <50 mg in some patients; eligibility was assessed at Screening 2b.

Abbreviations: BMI, body mass index; BSA, body surface area; FAS(new)b, full analysis set ([patients newly recruited to] Phase 3b); GM, gravimetric measurement; N, number of patients; NA, not applicable.

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

2.4.1 Hyp1-18/2016 planned and actual enrolment, trial populations and analysis sets

Number of patients (total and for each treatment) planned and analyzed[29]:

- Phase 3a: planned 150 patients
- Phase 3b: planned 500 patients (including roll-over patients from the Phase 3a part)

Table 6: Trial populations from Hyp1-18/2016

		Number of patients	
Phase 3a part	**1% GPB**	**Placebo**	**Total**
SAFa	87	84	171
FASa	87	84	171
PPSa	69	58	127
Phase 3b part			
SAFb	518	NA	518
FASb	518	NA	518
PPSb	326	NA	326
FASnewb	357	NA	357
PPSnewb	205	NA	205
Phase 3a plus 3b part			
SAF*	524	4	528

*Source:Hyp-18/2016 Phase3a/b CSR [29]
Notes: * All patients of SAFa plus all patients in the FASnewb
Abbreviations: FASa/b, full analysis set (Phase 3a/3b); FASnewb, full analysis set (patients newly recruited to Phase 3b); GPB, glycopyrronium bromide; N, number of patients; NA, not applicable; PPSa/b, per-protocol set (Phase 3a/b); PPSnewb, per-protocol set (patients newly recruited to Phase 3b); SAF(a/b), safety analysis set (Phase 3a/3b).

2.4.2 Analysis sets

Safety analysis set (SAF)

The **SAF** includes all patients who received at least 1 dose of IMP in any phase of the study, i.e. all patients from the Phase 3a part and patients newly recruited to the Phase 3b part.[29] The **SAFa** includes all patients who received at least 1 dose of IMP in the Phase 3a part. The assignment of patients to the treatment groups was as actually treated. The SAFa was used for all safety analyses of the Phase 3a part. [29] The **SAFb** includes all patients treated at least once with IMP in the Phase 3b part of the study (i.e. roll-over patients from the Phase 3a and patients newly recruited to the Phase 3b part) and was used for all safety analyses of the Phase 3b part.[29]

Full analysis set (FAS)

The **FASa** includes all patients randomised and treated at least once with IMP in the Phase 3a part. As per the intention-to-treat principle, the assignment of patients to the treatment groups was as randomised. The FASa was used for the evaluation of all efficacy endpoints of the Phase 3a part.[29]

The **FASb** includes all patients of the SAFb.[29]

The **FASnewb** includes all patients newly recruited to the Phase 3b part who were treated at least once with IMP. This set is a subset of the FASb and was used for the evaluation of the primary and all secondary endpoints regarding only newly recruited patients. The FASb was used for all other secondary endpoint analyses.[29]

Per-protocol set (PPS)

The **PPSa** includes all patients of the FASa without any major protocol deviations in the Phase 3a part. The assignment of patients to the treatment groups was as actually treated. Protocol deviations were reviewed during a blind data review meeting (BDRM) held before the data base lock and unblinding of the Phase 3a part data to identify major deviations leading to the exclusion of patients from the PPSa.[29]

The **PPSb** or **PPSnewb** includes all patients of the FASb or FASnewb who had no major protocol deviations until Week 28. No analyses using the PPSb or PPSnewb were planned after Week 28. Protocol deviations were reviewed during a data review meeting (DRM) held before the final data base lock to identify major deviations leading to the exclusion of patients from the PPSb or PPSnewb. ‘Use of forbidden medication’ was the only protocol deviation defined *a priori* as major deviation for both study parts. The PPSa, PPSnewb, and PPSb were used for the sensitivity analyses of the primary endpoint and for selected analyses of secondary endpoints.[29] The statistical plan is summarised in Table 7.

2.4.3 Statistical analysis plan

Table 7: Summary of statistical analysis plan

Sample size calculation	For the Phase 3a part, a sample of N = 63 per group was sufficient to detect an effect size of 0.5 between the placebo and the 1% GPB in sweat production with a power = 0.9 and α = 0.05 using a 2-sided t-test. Considering dropouts (about 15%), a sample size of N = 75 per group was calculated. For the long-term part, a sample size of 500 patients was considered sufficient to assess the safety of 1% GPB cream.
Method of assigning patients to treatment groups	Patients were randomly assigned dispensers containing 1% GPB or placebo cream by a computer-generated randomization list with a 1:1 allocation. The randomization was done centrally with no stratification and with permutated blocks. To ensure a balanced treatment allocation within centers, dispensers were supplied to each study center as multiples of randomization blocks. At the study center, eligible patients were assigned numbers in ascending order beginning with the lowest available number. During the double-blind Phase 3a part of the study, study participants, investigators, the sponsor, and all other persons involved in the conduct of the study were blinded to the treatment. To maintain the blind, the 1% GPB and the placebo cream had identical appearance, texture, and smell, and were labeled and packaged identically. To minimize the potential for bias, treatment randomization information was kept confidential by the responsible sponsor personnel and was not disclosed to the investigator, other study center personnel, the sponsor or its designee, and clinical research associate until after database lock.
Statistical analyses	The statistical analyses were performed separately for the double-blind, dose-confirming Phase 3a part of the study, and for the open-label, long-term Phase 3b part of the study. The full analysis set for Phase 3a (FASa) included all patients randomized and treated at least once with the IMP after randomization. In accordance with the intention-to-treat principle, the assignment of patients to the treatment groups was as randomized. Confirmatory hypothesis tests are performed for the primary and key secondary efficacy endpoints in the Phase 3a and the long-term part of the study. Because the confirmatory efficacy analysis of the long-term part of the study will not use data from the Phase 3a part of the study, no α adjustment for the primary efficacy analysis in the Phase 3a part was considered necessary.

	Key secondary endpoints are tested hierarchically to ensure strong control of the family-wise error rate (multiple type I-error level) of 5% (2-sided). All patients were treated as planned and analyzed as treated. Analyses were carried out as described in the statistical analysis plan which is based on the protocol. The primary endpoint (absolute change in total sweat production from Baseline to Day 29) of this Phase 3a part was tested with a mixed model including the baseline value as fixed effect and center as random effect. The model is based on the logarithmic values of total sweat production as the results of the Phase 1b study showed a skewed distribution of absolute values and absolute changes from Baseline values. Missing gravimetric measurements at Baseline were imputed using the Screening value. Missing gravimetric values at day 29 were not imputed for the main analysis. The key secondary endpoints were tested with the Cochran-Mantel-Haenszel test (HDSS responder) or the van Elteren 2-sample test (HidroQoL) both stratified by center. All further secondary endpoints were analyzed exploratory using non-parametric tests, i.e., Wilcoxon signed rank tests, van Elteren 2-sample test or Cochran-Mantel-Haenszel test depending on the endpoint. All tests were performed on a significance level of 5% (2-sided). No missing values regarding (further) secondary endpoints were imputed. The primary endpoint of the Phase 3b part, change in total sweat production from baseline (day 1) to week 12, was only assessed in newly recruited patients, and was tested with a mixed effects model with mean centred logarithmic baseline values as fixed effects and centre as random effect at a significance level of 2.94% (α = 0.0294; 2-sided). The key secondary endpoints of Phase 3b were tested hierarchically with a 1-sample binomial test (HDSS responder) at a significance level of 1.47% (α = 0.0174, 1-sided) or the Wilcoxon signed rank test (HidroQoL) at a significance level of 2.94% (α = 0.0294, 2-sided). Further secondary endpoints were tested on a significance level of 5% (2-sided). The significance level for the final and the interim analysis of the long-term part of the study are split equally using the Pocock boundaries for two planned analyses to meet a global significance level of 5%. Confirmatory hypothesis tests were performed hierarchically until the first non-significant test result was obtained for the respective primary and key secondary efficacy endpoints.

Source:Hyp-18/2016 Phase3a/b CSR [29]
Abbreviations: FASa, full analysis set (Phase 3a); GPB, glycopyrronium bromide; HDSS, hyperhidrosis disease severity scale; HidroQol, hyperhidrosis quality of life index; IMP; investigational medicinal product; N, number of patients.

2.5 Critical appraisal of the relevant clinical effectiveness evidence

The Phase 3a/3b study for 1% GPB cream (Hyp-18/2016 Phase 3a/3b) was critically appraised using the Systematic reviews: Centre for Reviews and Dissemination's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination). Quality assessment of the Hyp-18/2016 Phase 3a/3b GPB study is provided in Table 8 and Table 9.

Table 8: Hyp1-18/2016 Phase 3a critical appraisal

	Hyp1-18/2016 Phase 3a[24]
Was randomisation carried out appropriately?	Yes - patients were randomly assigned dispensers containing 1% GPB or placebo cream by a computer-generated randomisation list with a 1:1 allocation. The randomization was done centrally with no stratification and with permutated blocks with a block size of 4.
Was the concealment of treatment allocation adequate?	Yes - to ensure a balanced treatment allocation within centres, dispensers were supplied to each study centre as multiples of randomisation blocks. At the study centre, eligible patients were assigned numbers in ascending order beginning with the lowest available number
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes – no significant differences between the GPB 1% cream and placebo study groups, in sex, age, height, weight, body mass index, body surface area, or baseline sweat production.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes - to maintain the blinding, the GPB 1% cream and the placebo cream had identical appearance, texture, and smell, and were labelled and packaged identically. treatment randomisation information was kept confidential by the responsible sponsor personnel and was not disclosed to the investigator, other study centre personnel, the sponsor or its designee, and clinical research associate until after database lock for the interim analysis. No premature breaking of the code was necessary.
Were there any unexpected imbalances in dropouts between groups?	No – 3 patients in the GPB 1% treatment group withdrew and 2 patients in the placebo group
Is there any evidence to	No – outcomes measured were pre-specified

suggest that the authors measured more outcomes than they reported?	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes – this is the Full analysis set (FAS) population for the study. Patients with missing values at Baseline or Day 29 were considered non-responders for the HDSS secondary endpoint. Post hoc analysis was conducted for this endpoint excluding missing values from the analysis.
Was there good quality assurance for this study?	Yes –Study was conducted in compliance with the Declaration of Helsinki and in compliance with IEC and ICH GCP guidelines

Source: Hyp-18/2016 Phase3a/b CSR[29]
Abbreviations: CSR, clinical study report; GCP, good clinical practices; FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, hyperhidrosis disease severity scale; IEC, International electrotechnical commission; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

Table 9: Hyp1-18/2016 Phase 3b critical appraisal

	Hyp1-18/2016 Phase 3b[25]
Was the cohort recruited in an acceptable way?	Yes – The cohort was rolled from the 3a study or were newly recruited
Was the exposure accurately measured to minimise bias?	Yes – diary entries to capture number of applications of GPB 1% cream per week during each of first 4 weeks and at weeks 8, 12, 28, 52 and 72
Was the outcome accurately measured to minimise bias?	Yes – The study was monitored by the CRO to ensure that it was conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements. Clinical monitors checked completeness, clarity, and consistency of the data recorded in the eCRFs/CRFs for each participant, and adherence to the protocol and to GCP. Audits, independent of and separate from the routine monitoring and quality control functions, were carried out as part of the implementation of QA to ensure that the study was conducted in compliance with the protocol, SOP, GCP, and all applicable

	regulatory requirements. Additional QA procedures were performed at study sites and during data management to assure that safety and efficacy data were adequate and well documented
Have the authors identified all important confounding factors?	Yes – These are addressed in the 3a and 3b exclusion criteria
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes – Exclusion criteria were developed to avoid confounding factors from other active treatments
Was the follow up of patients complete?	Yes – Patients received treatment for 72 weeks with a 4-week follow-up as per protocol. Protocol violations were recorded and patients excluded
How precise (for example, in terms of confidence interval and p values) are the results?	Very Precise – Actual probability values reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001

Source:Hyp-18/2016 Phase3a/b CSR [29]
Abbreviations: CSR, clinical study report; eCRF, electronic case report form; CRF, case report form; CRO, contract research organization; GCP, good clinical practices; GBP, glycopyrronium bromide; SOP, standard operating procedure; QA, quality assurance.Clinical effectiveness results of the relevant studies

2.6 Clinical effectiveness results of the relevant studies

Summary

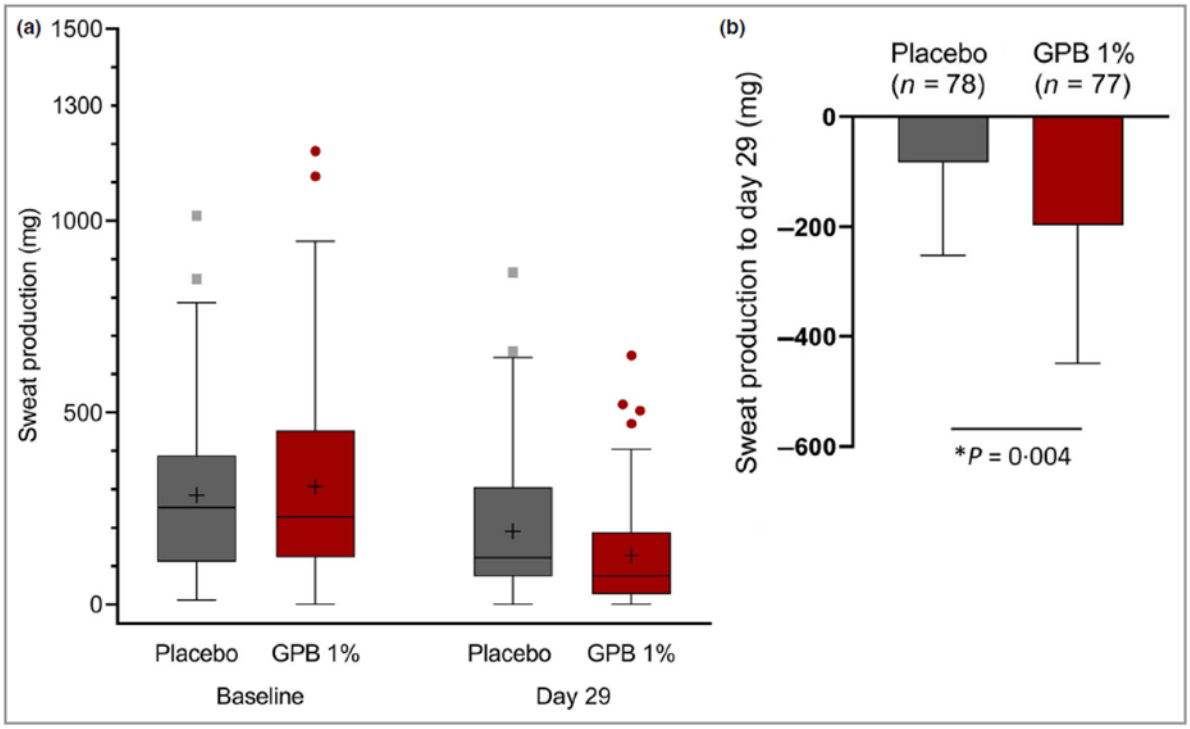
- As observed in both study parts,[24,25] GPB 1% cream significantly reduces sweat production in patients with severe primary axillary hyperhidrosis after 4 weeks of once-daily treatment.
- The reduction of sweat production as measured by gravimetry is maintained throughout the assessed period (up to Week 12) even when the application frequency of the GPB 1% cream was reduced (with a median of 7 applications per week at Week 4 and 4 applications per week at Week 12).
- GPB 1% cream continuously improved the severity of hyperhidrosis (as assessed by the HDSS) and the patient's quality of life (as assessed by the HidroQoL, and DLQI) over a period of up to 72 weeks.
- Efficacy results of the first 4 weeks of treatment of the Phase 3a and Phase 3b part were very similar, and confirmed the reproducibility and robustness of the treatment effect.

2.5.1 Hyp1-18/2016 Phase 3a

2.5.1.1 Primary outcome | Gravimetrically assessed sweat production

Mean sweat production was reduced by 197.08 mg for the GPB 1% cream group and 83.49 mg for the placebo group. Absolute reduction in sweat production from baseline to day 29 in logarithmic values was statistically significantly larger in the GPB 1% cream group than in the placebo group (P = 0.004; mixed-effects model). Hence, the primary endpoint of the study was met (Figure 6).[24]

Figure 6: (a) Absolute sweat production (mg) in 5 min as measured by gravimetry at baseline and day 29 (b) Change in sweat production from baseline to day 29



Source: Abels *et al.* 2021[24]
(a) Absolute sweat production (mg) in 5 min as measured by gravimetry at baseline and day 29. Data are shown for the full analysis set (n = 171). Boxes represent the lower and upper quartile; median values are indicated by the horizontal lines, mean values by a '+', and upper and lower whiskers indicate the maximum and minimum values (excluding outliers). Outliers are shown as grey rectangles (placebo) or red circles [(GPB) 1%]. (b) Change in sweat production from baseline to day 29. Data are shown as mean (SD) for the full analysis set (n = 171: 84 in the placebo group and 87 in the GBP 1% group). *Statistically significant (P-value for treatment effect is based on the mixed model using the absolute change in logarithmic values of sweat production).
Abbreviations: GPB, glycopyrronium bromide; mg, milligram; n, number of patients.

2.5.1.2 Secondary outcomes | Patient reported outcomes

HDSS showed a change from baseline that clearly favoured GPB 1% cream treatment over placebo at day 15 (difference in median –1.0; P = 0.002) and day 29 (P = 0.014; Table 3). Median improvement in HidroQoL total score was significantly greater for GPB 1% cream (–6.0 points) than for placebo (–1.0 point; P < 0.001) on day 29. Similar results were observed for the individual domains of daily life activity and psychosocial life. The impact of axillary hyperhidrosis on QoL was also determined using the DLQI. Here, the median improvement at day 15 was larger for patients in the GPB 1% group (–5.0 points) than for placebo (–2.0 points). The improvement seen for the GPB 1% cream was upheld until day 29. The difference in median between the GPB 1% cream and placebo was statistically significant at both timepoints (P = 0.002 and P = 0.003, respectively).

Table 10: Absolute change in patient-reported outcome measure tool from baseline to days 15 and 29

	Change from baseline median (95% CI)		
	Placebo (n = 84)	GPB 1% cream (n = 87)	GPB 1% cream vs. placebo P-value
HDSS			
Median baseline (range)	4·0 (3–4)	3·0 (2–4)[a]	
Day 15	0·0 (0·0 to 0·0)[b, *]	–1·0 (–1·0 to 0·0)[c, *]	0·002
Day 29	0·0 (0·0 to 0·0)[d, *]	0·0 (–1·0 to 0·0)[e, *]	0·014
HidroQoL©			
Median baseline (range)	30·0 (11·0–36·0)[f]	29·0 (10·0–36·0)[g]	
Day 15	–1·0 (–2·0 to –1·0)[b *]	–5·0 (–8·0 to –2·0)[h *]	< 0·001
Day 29	–1·0 (–2·0 to –1·0)[b *]	–6·0 (–9·0 to –4·0)[c *]	< 0·001
DLQI			
Median baseline (range)	15·0 (0·0–28·0)[e]	14·0 (0·0–30·0)	
Day 15	–2·0 (–3·0 to –1·0)[b *]	–5·0 (–7·0 to –2·0)[h *]	0·002
Day 29	–3·0 (–4·0 to –1·0)[b]	–5·0 (–8·0 to –4·0)[c]	0·003

Source: Abels *et al.* 2021[24]
Notes: [a]n = 86; [b]n = 79; [c]n = 84; [d]n = 80; [e]n = 83; [f]n = 81; [g]n = 87; [h]n = 85. *P < 0·0001.
Abbreviations: CI, confidence interval; DLQI, dermatology life quality index; GPB, glycopyrronium bromide; HDSS, hyperhidrosis disease severity scale; HidroQoL, hyperhidrosis quality of life index.

2.5.1.3 Secondary outcome | Responder analysis

The proportion of responders to treatment was determined based on gravimetrically measured sweat production, as well as on the HDSS and HidroQoL questionnaires. At day 29, significantly more patients achieved a reduction in sweat production of > 50%, 75% or 90% with GPB 1% cream than with placebo. More than half of patients achieved a 50% reduction in sweating with the GPB 1% cream [58% (n = 50) vs. 35% (n = 29) with placebo], while nearly one in four achieved a reduction in sweat of 90% [23% (n = 20) vs. 10% (n = 8) with placebo].[24] Overall, the proportion of patients achieving a certain degree of sweat reduction was approximately twofold higher for the GPB 1% cream than for placebo (1.7-fold for a 50% reduction and 2.4-fold for a 90% reduction). Based on the HDSS, more patients in the GPB 1% group experienced a response to treatment (for day 29). At day 15 there was a

significantly higher proportion of patients with an improvement of ≥ 2 points than for placebo [25% (n = 22) vs. 9.5% (n = 8); P = 0.007], while at day 29 the responder rate was similar [23% (n = 20) vs. 12% (n = 10)] and the difference between the groups approached statistical significance (P = 0.054). The proportion of HidroQoL responders with GPB 1% cream [60% (n = 52)] vs. placebo [26% (n = 22); P < 0.001] was significant, as determined in a post hoc analysis (MCID ≥ 4).[24]

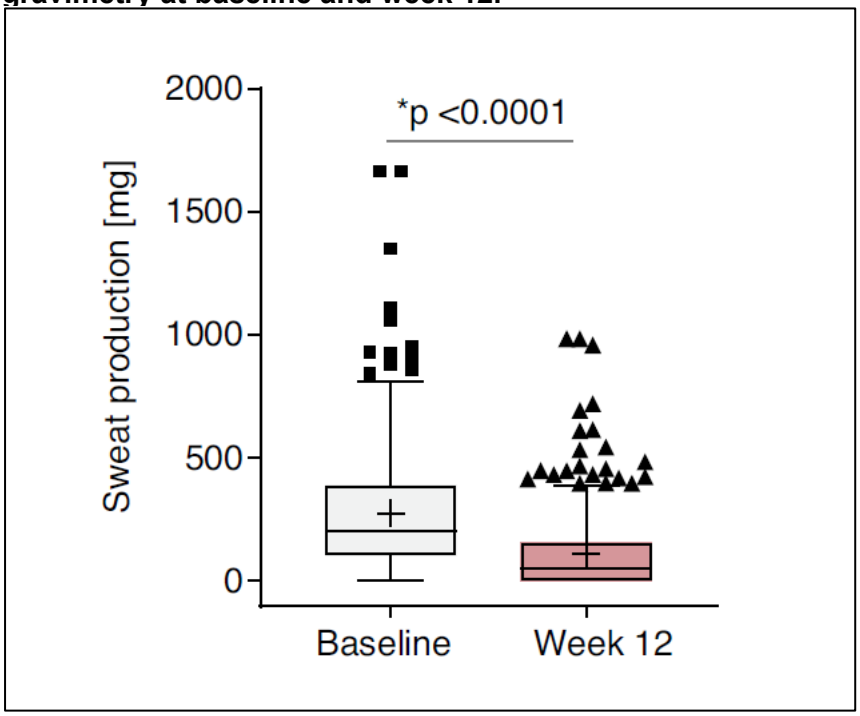
2.5.2 Hyp1-18/2016 Phase 3b

A total of 518 patients was treated with GPB 1% cream for 72 weeks.[25] Of these patients, 161 patients rolled over from the preceding Phase 3a trial[24] and 357 new patients were enrolled according to the inclusion criteria.

2.5.2.1 Primary Outcome | Gravimetrically assessed sweat production

Median total sweat production assessed by GM was 212.4 mg at baseline and 75.8 mg after 12 weeks of treatment with GPB 1% cream. Absolute change in logarithmic values was statistically significant (p < 0.0001; mixed effects model), thus the primary endpoint of the study was met (Figure 7).[25]

Figure 7: Absolute sweat production (mg) in 5 min as measured by gravimetry at baseline and week 12.



Source: Szeimies *et al.* 2022[25]
Data are shown for the full analysis set of newly recruited patients (FASnewb) (N = 357). Boxes represent the lower and upper quartile; median values are indicated by the horizontal lines, mean values by a '+', and upper and lower whiskers indicate the maximum and minimum values (excluding outliers). Outliers are shown as black rectangles (baseline) or black triangles (week 12). *Statistically significant (p-value for treatment effect is based on the mixed model using the absolute change in logarithmic values of sweat production).
Abbreviations: FAS, full analysis set; mg, milligram.

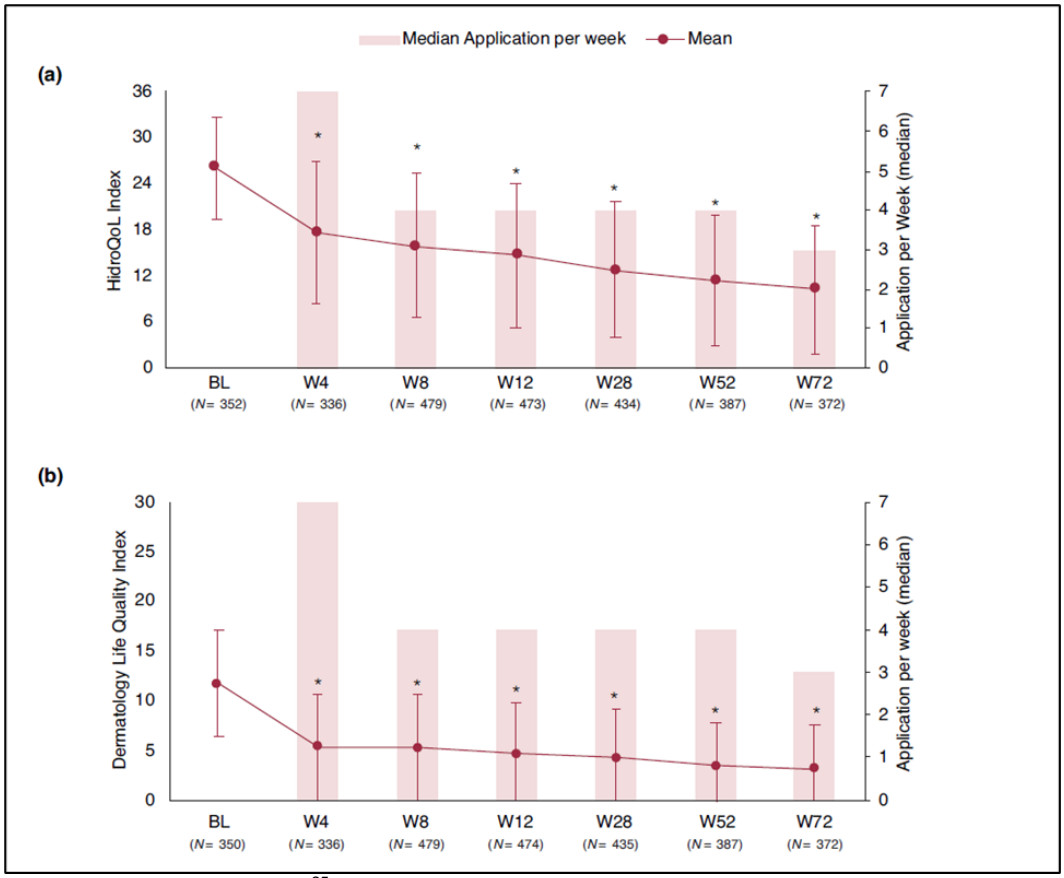
2.5.2.2 Secondary outcomes | Patient reported outcomes

HidroQoL total score (median change: −11.0), as well as the daily life activities (median change: −5.0) and psychosocial domains (median change: −6.0), improved from baseline to week 12 with statistical significance in the FASb ($p < 0.0001$) as well as in PPS. Significant decreases in HidroQoL total scores were observed for all study time points ($p < 0.0001$), meaning that patients' QoL improved significantly compared to baseline.[25]

There was a decrease in median absolute change in DLQI score of 6 (week 4), 7 (week 8), 7 (week 12), 8 (week 28), 9 (week 52) and 10 (week 72) compared with baseline values ($p < 0.0001$ for all time points) . Overall, significant decreases in DLQI scores were observed for all study time points ($p < 0.0001$), pointing to a considerable ongoing improvement in the patients' quality of life starting as early as 4 weeks after the first treatment with GPB 1% cream. The higher the DLQI score, the more impaired are the patients in their daily life. Therefore, a decrease show that patients' QoL had improved.[25]

All changes after week 4 were seen even though the median application frequency was decreased (seven applications per week at week 4 to three applications per week at week 72).

Figure 8: (a) Absolute values in the HidroQoL from baseline to weeks 4, 8, 28, 52 and 72. (b) Absolute values in the DLQI from baseline to weeks 4, 8, 12, 28, 52 and 72.



Source: Szeimies *et al.* 2022[25]
Abbreviations: BL, baseline; DLQI, dermatology life quality index; HidroQoL, hyperhidrosis quality of life index; N, number of patients; W, week.

2.5.2.3 Secondary outcome | Treatment responders

Patients who had a ≥2-point improvement in the HDSS assessment compared to baseline values were defined as responders to treatment. For the key secondary end point, percentage of responders should be greater than 25%. At week 12, although 28% of patients responded to treatment, the difference to baseline did not reach statistical significance for FAS (p = 0.0579). However, the proportion of responders was significant at week 28 (29%, p = 0.0112) and onwards (30%, p = 0.0072 and 32%, p = 0.0002 for week 52 and week 72, respectively). In addition, key secondary endpoint, at week 12 was statistically significant for the per protocol set (PPS, N = 326; p = 0.003) and week 28 (PPS, N = 326; p < 0.0001).[25]

Table 11: HDSS responders at week 12 and 28 in FASb (N = 518) and change in the HidroQoL from baseline to week 12

Key secondary endpoints - HDSS responders and change in HidroQoL (FASb) (N=518)	
HDSS responders (≥2-point improvement from Baseline to Week 12) - >25% responders	
Responders, N (%)[a]	145 (28.0)
Proportion (CI)[b] p-value[c]	0.28 (0.23; 0.33) 0.0579
HDSS responders (≥2-point improvement from Baseline to Week 28) - >25% responders	
Responders, N (%)[a]	152 (29.3)
Proportion (CI)b	0.29 (0.25; 0.35)
p-value[c]	0.0112
Change in the HidroQoL from Baseline to Week 12	
Total score	
Baseline a, median (range)	30.0 (10 - 36)[f]
Baseline b, median (range)	27.0 (4 - 36)[g]
Median change to Week 12 (CI)[d]	-11.0 (-13.0; -10.0)[h]
p-value[e]	<0.0001
Daily life activities domain score	
Baseline a, median (range)	11.0 (2 - 12)[f]
Baseline b, median (range)	10.0 (1 - 12)[g]
Median change to Week 12 (CI)[d]	-5.0 (-5.0; -4.0)[h]
p-value[e]	<0.0001

Psychosocial domain score	
Baseline a, median (range)	19.0 (7 - 24)[f]
Baseline b, median (range)	17.0 (0 - 24)[g]
Median change to Week 12 (CI)[d]	-6.0 (-7.0; -5.0)[h]
p-value[e]	<0.0001

Source: Szeimies *et al.* 2022[25]

Notes: Patients with missing values were considered non-responders. [a]Percentages are based on the number of patients in each analysis set. [b]Clopper-Pearson, exact 1-sided 98.53%. [c] 1-sample binomial test, 1-sided, α = 0.0147. [d] Hahn-Meeker, 97.06%. [e]Wilcoxon signed rank test, 2-sided, α = 0.0294. [f] N = 160. [g] N = 352. [h] N = 468.

Abbreviations: CI, confidence interval; FASb, full analysis set (Phase 3b); HDSS, hyperhidrosis disease severity scale; HidroQoL, hyperhidrosis quality of life; N, number of patients.

2.5.3 Subsequent treatments used in the relevant studies

After the follow up visit patients were not followed up after stopping treatment with GPB 1% cream.

2.7 Subgroup analysis

There were no subgroup analyses in the Hyp-18/2016 Phase 3a/3b trial[24,25] relevant to the CS. Subgroup analyses are provided in the Clinical Study Reports provided by the Company.

2.8 Meta-analysis

There were no meta-analyses in the Hyp-18/2016 Phase 3a/3b trial[24,25] relevant to the CS.

2.9 Indirect and mixed treatment comparisons

Comparative efficacy between GPB 1% cream and relevant comparators is estimated using Bucher indirect treatment comparisons (ITCs) anchored through a placebo arm.[30] This method helps minimise bias across studies by preserving the benefits of randomisation and providing a consistent baseline for estimating treatment effects. Given the limited evidence base in this disease area and due to the lack of access to patient-level data from the GPB 1% cream trials, the Bucher approach was selected for its simplicity and ease of interpretation, more advanced methods were either considered impossible or unlikely to yield robust estimates of relative efficacy.

The ITC uses data from the Phase 3a study for GPB 1% cream,[24,29] from Schollhammer et al. (2015) for antimuscarinics,[26] and from Lowe et al. (2007) for botulinum toxin.[27] A scenario analysis uses the odds ratios (ORs) estimated from a network meta-analysis (NMA) published in Wade et al. (2017) for medications (antimuscarinics) vs. placebo and botulinum toxin vs. placebo for the HDSS score ≥2 improvement.[18]

2.5.4 Summary of studies included in the ITCs

2.5.4.1 GPB 1% cream

The Phase 3a clinical data are used to inform the relative efficacy of GPB 1% cream compared to placebo – these data reflect randomised controlled data across a 29 day period (Section 2.3.2). From the Phase 3a study, outcomes are available for the number of responders defined by ≥2 point improvement in Hyperhidrosis Disease Severity Scale (HDSS) score at day 15 and 29 in the full analysis set (FAS) population (FASa) and at day 29 in the per-protocol set (PPS) population (PPSa), and the number of responders defined by ≥1 point improvement in HDSS score at day 29 in FASa (Table 12).

Table 12: GPB 1% cream HDSS outcomes | Phase 3a

	Population	Timepoint	Endpoint	n	N	OR
GPB 1% cream	FASa	Day 15	≥2	[redacted]	[redacted]	[redacted]
Placebo				[redacted]	[redacted]	
GPB 1% cream	FASa	Day 29	≥2	[redacted]	[redacted]	[redacted]
Placebo				[redacted]	[redacted]	
GPB 1% cream	PPSa	Day 29	≥2	[redacted]	[redacted]	[redacted]
Placebo				[redacted]	[redacted]	
GPB 1% cream	FASa	Day 29	≥1	[redacted]	[redacted]	[redacted]
Placebo				[redacted]	[redacted]	

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; N, number; OR, odds ratio; PPS, per protocol set.
Source: Table 20, Table 34, Table 41, Table 4.3.4_b, Table 4.4.3_b, and Table 6_b, CSR

2.5.4.2 Antimuscarinics

As described in Appendix B, no placebo-controlled data are available for antimuscarinics (including propantheline bromide, oxybutynin, or oral GPB) in patients with severe PAHH. When the search was broadened to include all types of HH, six studies were identified for oxybutynin, but none for propantheline bromide or oral GPB. The SLR presented in Appendix B aligns with the findings of a published SLR and meta-analysis of randomised controlled trials (RCTs) assessing the efficacy and safety of oxybutynin in patients with HH (El-Samahy et al., 2023; search date: June 2022).[31] No new relevant studies have been published since that search date.

Of the six placebo-controlled oxybutynin studies identified, only two report outcomes in terms of HDSS response:

- Ghaleiha et al. (2012) evaluated oxybutynin in patients with HH secondary to sertraline use (prescribed for depression).[32] Only 40% of patients in the oxybutynin arm had AHH.

The study reported the distribution and mean HDSS scores at baseline and 2 weeks post-treatment.

- Schollhammer et al. (2015) assessed oxybutynin in patients with localised or generalised HH.[26] In this study, 75% of patients in the oxybutynin group had AHH. Outcomes included ≥1, 1-, 2-, and 3-point improvements in HDSS scores after 6 weeks. Statistically significant odds ratios were observed for both ≥1-point and ≥2-point improvements versus placebo. No patients experienced a worsening of HDSS scores.

Given that Ghaleiha et al. (2012) focused on patients with secondary HH due to antidepressant use, this population does not align with the target population of the current appraisal. As such, these data are excluded from the ITCs.

The remaining relevant study (Schollhammer et al. (2015)) is summarised in Table 13, with HDSS response outcomes presented in Table 14. In the absence of alternative data, efficacy results for oxybutynin from this study are assumed to represent the effectiveness of antimuscarinic treatments overall. This approach is consistent with the published NMA by Wade et al. (2017) in the Centre for Reviews and Dissemination Health Technology Assessment, where all oral treatments for HH were grouped as a single category.[18] This assumption is further supported by feedback from UK clinical experts involved in the Wade et al. (2017) study, who indicated that the effectiveness of different medications was generally comparable.

The published NMA incorporates data from Mehrotra et al. (2015) and Muller et al., which evaluated 2% or 4% unlicensed GPB wipes and methantheline bromide versus placebo in patients with axillary or palmar HH.[33,34] These studies are not included in the ITCs presented in this submission as treatments are not reflective of those available and used in UK clinical practice. Wade et al. (2017) found no eligible studies for propantheline bromide, oxybutynin, or oral glycopyrrolate based on their SLR criteria. However, clinical expert input confirmed that the effectiveness across medications was broadly similar. As a result, efficacy data from the available studies were assumed to represent all medications versus placebo. The NMA estimated an OR of 7.21 (95% CI: 1.56–53.83) for achieving a ≥2-point improvement in HDSS at 4 weeks, which is used in a scenario analysis within the model.

Table 13: Summary of Schollhammer et al. (2015) | Source of HDSS data for oxybutynin in HH[26]

Study	Type	Country	Type of HH	Site of HH†	Baseline HDSS‡	Treatment	N	HDSS outcomes
Schollhammer et al. (2015)	Prospective RCT	France	localised: 5 (17%), generalised: 25(83%)	Palmar: 22 (69%), planter: 22 (69%), axillary 24 (75%), fascial: 7 (22%), truncal 13 (41%)	2: 3(10%), 3: 17(57%), 4: 10(33%)	Oxybutynin day 1 to 4: 2.5 mg, day 5 to 7: 5 mg, day 8 to the end of the six weeks: 7.5 mg	30	≥1 improvement in HDSS 1, 2, and 3 point improvement in HDSS No change in HDSS Worsening of HDSS
			localised: 5 (17%), generalised: 25(83%)	Palmar: 14 (47%), planter: 17 (57%), axillary 21 (70%), fascial: 12 (40%), truncal 13 (43%)	2: 2(7%), 3: 18(60%), 4: 10(33%)	Placebo	32	

Abbreviations: HDSS, hyperhidrosis disease severity scale; HH, hyperhidrosis; mg, milligrams; N, number; RCT, randomised controlled trial † Percentages for HH sites may exceed 100% as patients could have multiple affected sites. ‡ HDSS is scored from 1 (mild) to 4 (severe)

Table 14: Oxybutynin HDSS outcomes | Schollhammer et al. (2015)[26]

	Population	Timepoint	Endpoint	n	N	OR
Oxybutynin	Schollhammer et al. (2015)	6 weeks	≥2	13	30	0.09 (0.02 - 0.43)
Placebo				2	32	
Oxybutynin	Schollhammer et al. (2015)	6 weeks	≥1	18	30	0.22 (0.08 - 0.66)
Placebo				8	32	

Abbreviations: HDSS, hyperhidrosis disease severity scale; N, number; OR, odds ratio

2.5.4.3 Botulinum toxin

As outlined in Appendix B, six placebo-controlled studies have evaluated the efficacy of botulinum toxin in patients with severe PAHH. Among these, only two studies (Lowe et al. (2007) and Lee et al. (2022)) report response using the HDSS:

- Lowe et al. (2007) compared HDSS outcomes across three arms: botulinum toxin 50U per axilla, 75U per axilla, and placebo, in patients with severe PAHH (see Table 15).[27] The study reported the proportion of patients achieving a ≥2-point improvement in HDSS score at 4 weeks after both the first and second treatments, as well as the duration of treatment effect. The results showed statistically significant ORs in favour of botulinum toxin over placebo, with minimal differences observed between dosage groups or between patients receiving first versus repeat treatments. Table 16 summarises the HDSS response outcomes from Lowe et al. (2007).
- Lee et al. (2022) compared HDSS response across two arms: botulinum toxin 50U per axilla and placebo in patients with severe PAHH.[35] The study reported the proportion of patients achieving a ≥2-point improvement in HDSS score at 4, 8, 12, and 16 weeks. Botulinum toxin A was shown to be statistically better than placebo at all time points. The data from Lee et al. (2022) were not included in the ITCs informing this appraisal, as the study was conducted exclusively in Korean centres. As such, its applicability to UK clinical practice is limited.

The SLR presented in Appendix B is consistent with the findings of a previously published SLR and meta-analysis of RCTs assessing botulinum toxin for both primary and secondary focal HH (Obed et al. (2021); search date: August 2020).[36] Note: Lee et al. (2022) was published after the published SLR. Therefore, this study was not reported in the published SLR.

The published NMA by Wade et al. (2017) includes data from Lowe et al. (2007) and Ohshima et al. (2013) for botulinum toxin versus placebo in patients with AHH.[37] Ohshima et al. (2013) was excluded from the SLR conducted for this appraisal, as the publication is in Japanese. Furthermore, the study's relevance to UK clinical practice is limited due to the use of patient-reported HDSS outcomes, which may be subject to cultural reporting differences between Japanese and UK populations.[38] The NMA estimated an odds ratio (OR) of 9.207 (95% CI: 4.73–18.1) for achieving a ≥2-point improvement in HDSS at 4 weeks. Although Ohshima et al. (2013) reported outcomes at 3 months, these were assumed to be comparable to 4-week data within the NMA. A scenario analysis explores the use of these data.

Table 15: Summary of Lowe et al. (2007) | Source of HDSS data for botulinum toxin in severe PAHH[27]

Study	Type	Country	Type of HH	Site of HH	Baseline HDSS†	Treatment	N	HDSS outcomes	Re-treatment
Lowe 2007	RCT	USA	Primary, severe	Axillae (bilateral)	3.5 +/- 0.5	Botulinum toxin 50U/axilla	104	Responders ≥2 at 4-weeks	Re-treatment was allowed no sooner than
					3.5 +/- 0.5	Botulinum toxin 75U/axilla	110	Responders ≥2 at 4-weeks after second treatment	8 weeks after the previous treatment session.
					3.5 +/- 0.5	Placebo (0.9% sodium chloride [2ml])	108		Duration of effect from initial and second treatment. Number of patients receiving 1-4 treatments.

Abbreviations: HDSS, hyperhidrosis disease severity scale; HH, hyperhidrosis; ml, millilitres; N, number; RCT, randomised controlled trial; U, units. † HDSS is scored from 1 (mild) to 4 (severe)

Table 16: Botulinum toxin HDSS outcomes | Lowe et al. (2007)[27]

	Population	Timepoint	Endpoint	n	N	OR
Botulinum toxin 50U	Lowe et al. (2007)	4 weeks after initial tx	≥2	78	104	0.11 (0.06 - 0.21)
Placebo				27	108	
Botulinum toxin 75U	Lowe et al. (2007)	4 weeks after initial tx	≥2	82	110	0.11 (0.06 - 0.21)
Placebo				27	108	
Botulinum toxin	Lowe et al. (2007)	4 weeks after initial tx	≥2	160	214	0.11 (0.07 - 0.19)
Placebo				27	108	
Botulinum toxin 50U	Lowe et al. (2007)	4 weeks after second tx	≥2	41	48	0.06 (0.02 - 0.16)

Placebo				18	68	
Botulinum toxin 75U	Lowe et al. (2007)	4 weeks after second tx	≥2	39	53	0.13 (0.06 - 0.29)
Placebo				18	68	
Botulinum toxin	Lowe et al. (2007)	4 weeks after second tx	≥2	80	101	0.09 (0.05 - 0.19)
Placebo				18	68	

Abbreviations: HDSS, hyperhidrosis disease severity scale; N, number; OR, odds ratio; U, units.

2.5.5 Methodology

The Bucher ITC method is a simple statistical approach used to estimate the relative efficacy of treatments that have not been directly compared in a head-to-head trial. It involves using a common comparator (e.g., placebo or an active treatment) that links two treatment arms, allowing for an indirect comparison between them. Bucher ITCs are conducted separately for GPB 1% cream vs. oxybutynin and for GPB 1% cream vs. botulinum toxin.

This approach assumes transitivity, meaning that the comparison between GPB 1% cream and oxybutynin or botulinum toxin is valid if the clinical and methodological characteristics from the GPB 1% cream vs. placebo and placebo vs. oxybutynin comparisons or placebo vs. botulinum toxin comparisons are similarly distributed.

2.5.6 Results

Table 17 presents the results of the Bucher ITCs for antimuscarinics and botulinum toxin versus GPB 1% cream.

For antimuscarinics vs. GPB 1% cream, the ORs are [redacted]. These results should be interpreted with caution due to substantial differences in the underlying study populations and the timepoints at which outcomes were measured, as detailed in Section 2.5.7. These discrepancies likely violate the assumptions required for the Bucher method and contribute to considerable uncertainty in the estimated treatment effects. This is further reflected in the wide confidence intervals surrounding the ORs.

For botulinum toxin vs. GPB 1% cream, the ORs are [redacted]. UK clinical experts indicate that botulinum toxin can be a highly effective treatment option for some patients.[12] However, a key limitation is that botulinum toxin has a known waning effect, and the data from Lowe et al. (2007) only report outcomes at a single timepoint (4 weeks), preventing an assessment of longer-term treatment durability. This contrasts with GPB 1% cream, which provides a sustained treatment effect over time – as supported by the data from the Phase 3b. As such, comparing these treatments at a single timepoint does not fully capture the differences in how treatment benefit is accrued e.g., botulinum toxin typically produces an initial strong response followed by waning, whereas GPB 1% cream is associated with a more consistent therapeutic effect. Additionally, the mechanisms of action for botulinum toxin and GPB 1% cream differ significantly. Botulinum toxin works by irreversibly cleaving proteins in presynaptic axon terminals to block acetylcholine release at the neuromuscular junction, thereby reducing sweat gland activity. Two possible mechanisms can explain the time limitation of the effect of botulinum toxin, namely turnover rate of the cleaved proteins and axonal sprouting. By contrast, GPB 1% cream acts locally as an anticholinergic agent on muscarinic receptors in the skin. This difference further limits the comparability of the two treatments. These challenges, along with the wide confidence intervals, highlights the uncertainty in the comparison.

Table 17: Bucher ITCs conducted[26,27,29]

#	Treatment	Source of data	Timepoint	HDSS response endpoint	OR (95% CI)
Antimuscarinics vs. GPB 1% cream					
1	GPB 1% cream	FASa	Day 29	≥2	[redacted]
	Antimuscarinics	Schollhammer et al. (2015)	6 weeks	≥2	
2	GPB 1% cream	PPSa	Day 29	≥2	[redacted]
	Antimuscarinics	Schollhammer et al. (2015)	6 weeks	≥2	
3	GPB 1% cream	FASa	Day 29	≥1	[redacted]
	Antimuscarinics	Schollhammer et al. (2015)	6 weeks	≥1	
4	GPB 1% cream	FASa	Day 29	≥2	[redacted]
	Antimuscarinics	Wade et al. (2017)	4 weeks	≥2	
Botulinum toxin vs. GPB 1% cream					
4	GPB 1% cream	FASa	Day 29	≥2	[redacted]
	Botulinum toxin 100U	Lowe et al. (2007)	4 weeks after initial tx	≥2	
5	GPB 1% cream	FASa	Day 29	≥2	[redacted]
	Botulinum toxin 150U	Lowe et al. (2007)	4 weeks after initial tx	≥2	
6	GPB 1% cream	FASa	Day 29	≥2	[redacted]
	Botulinum toxin	Lowe et al. (2007)	4 weeks after initial tx	≥2	

7	GPB 1% cream	FASa	Day 29	≥2	[redacted]
	Botulinum toxin 100U	Lowe et al. (2007)	4 weeks after second tx	≥2	
8	GPB 1% cream	FASa	Day 29	≥2	[redacted]
	Botulinum toxin 150U	Lowe et al. (2007)	4 weeks after second tx	≥2	
9	GPB 1% cream	FASa	Day 29	≥2	[redacted]
	Botulinum toxin	Lowe et al. (2007)	4 weeks after second tx	≥2	
10	GPB 1% cream	PPSa	Day 29	≥2	[redacted]
	Botulinum toxin 100U	Lowe et al. (2007)	4 weeks after initial tx	≥2	
11	GPB 1% cream	PPSa	Day 29	≥2	[redacted]
	Botulinum toxin 150U	Lowe et al. (2007)	4 weeks after initial tx	≥2	
12	GPB 1% cream	PPSa	Day 29	≥2	[redacted]
	Botulinum toxin	Lowe et al. (2007)	4 weeks after initial tx	≥2	
13	GPB 1% cream	PPSa	Day 29	≥2	[redacted]
	Botulinum toxin 100U	Lowe et al. (2007)	4 weeks after second tx	≥2	
14	GPB 1% cream	PPSa	Day 29	≥2	[redacted]
	Botulinum toxin 150U	Lowe et al. (2007)	4 weeks after second tx	≥2	
15	GPB 1% cream	PPSa	Day 29	≥2	[redacted]
	Botulinum toxin	Lowe et al. (2007)	4 weeks after second tx	≥2	
16	GPB 1% cream	FASa	Day 29	≥2	[redacted]

Botulinum-toxin	Wade et al. (2017)	4 weeks	≥2

Abbreviations: CI, confidence interval; FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ITC, indirect treatment comparison; N, number; OR, odds ratio; PPS, per-protocol set; U, units

2.5.7 Uncertainties in the indirect and mixed treatment comparisons

Key uncertainties in the ITCs arise from differences in study populations and the timing of outcome assessments, both of which likely violate the assumptions underpinning the Bucher method and contribute to high uncertainty in the results. This uncertainty is further reflected by the wide confidence intervals around the effect estimates.

There are no placebo-controlled data available for antimuscarinics used in UK clinical practice in patients with severe PAHH. The only relevant evidence comes from Schollhammer et al. (2015), which evaluated oxybutynin in a broader HH population. Although most patients in this study had severe disease (90% in the oxybutynin arm, 93% in the placebo arm) and axillary involvement (75% and 70%, respectively), there are still a significant proportion of patients who are not comparable to the population in this appraisal. Another limitation is that Schollhammer et al. (2015) report efficacy only at 6 weeks, whereas the GPB 1% cream vs. placebo data extend only to 4 weeks, introducing further uncertainty due to the mismatch in assessment timepoints.

Due to the absence of placebo-controlled trials for other antimuscarinics relevant to UK clinical practice, the relative efficacy of oxybutynin from Schollhammer et al. (2015) is assumed to represent the class effect for all oral antimuscarinics. This approach is consistent with previous ITCs (e.g., Wade et al. (2017)). The ITC conducted by Wade et al. (2017) included two studies of antimuscarinics (Mehrotra et al. (2015) and Müller et al. (2013)) that are not relevant to current UK clinical practice, as they evaluated 2% or 4% unlicensed GPB wipes and methantheline bromide, which are not commonly used[33,34] or unavailable in the UK. Additionally, the Müller study did not report HDSS response data in a format directly usable in the ITC, so estimates had to be derived from continuous HDSS data. Despite its limitations, the NMA by Wade et al. (2017) reported an OR of 7.211 (95% CI: 1.56–53.83) for antimuscarinic medications versus placebo. In contrast, the OR derived from Schollhammer et al. (2015) is 11.5, indicating that the current analysis adopts a more conservative approach by assuming a higher treatment effect for antimuscarinics compared to the earlier ITC. This is demonstrated by the lower OR for antimuscarinics versus GPB 1% cream when using Wade et al. (2017) data, compared with Schollhammer et al. (2015): [redacted] versus [redacted], respectively, based on the FASa population and the ≥2-point HDSS improvement endpoint. Additionally, the wide confidence intervals reported in the published analyses underscore the high degree of uncertainty in making reliable relative treatment comparisons in this context.

The data from Lowe et al. (2007) provide a more robust comparison for botulinum toxin, as they are derived from a severe PAHH population and report outcomes at 4 weeks - aligned with the GPB 1% cream data. However, botulinum toxin is known to have a waning treatment effect, and the study only reports at one timepoint. Whilst additional analyses were performed using data from the second botulinum toxin treatment, these are limited by the truncated follow-up period, as acknowledged by the authors. The scenario analysis using the OR for botulinum toxin vs. placebo from the NMA published in Wade et al. (2017) demonstrates similar outcomes based on the FASa population and the ≥2-point HDSS improvement endpoint.

2.6 Adverse reactions

2.6.1 Hyp1-18/2016 Phase 3a

2.6.1.1 Compliance

Compliance was assessed in all patients who returned their dispensers by weighing the dispenser after return and relating the weight to the amount of product that should have been used over the 28 days according to the protocol. Patients treated with GPB 1% cream showed higher compliance regarding volume of product used than patients treated with placebo. The median number of applications per patient per week was [redacted] for the GPB 1% cream group and between [redacted] and [redacted] in the placebo group.[29]

2.6.1.2 Discontinuations

No patient discontinued due to an adverse event.[29]

2.6.1.3 Adverse events

The frequency and severity of adverse events (AEs), serious AEs (SAEs) and treatment-emergent AEs (TEAEs) were recorded. Using a skin reaction score, local tolerability at the application site was assessed by the investigator.

About half of patients in both study cohorts had at least one TEAE during the study (GPB 1% cream: 49%; placebo: 44%). Most TEAEs were mild or moderate. Most patients did not experience an adverse drug reaction (ADR) (87% placebo and 72% GPB 1%). The most common ADR was dry mouth (17%) and only a few other anticholinergic ADRs were reported. Application-site reactions [application-site dermatitis (1% in the GPB 1% group), application-site erythema (5% GPB 1% vs. 5% placebo), application-site pain (1% GPB 1% vs. 1% placebo), application-site papules (1% in the GPB 1% group) and application-site pruritus (1% GPB 1% vs. 1% placebo), none of which was treated] were reported in 9% of patients in the GPB 1% group and 7% of patients receiving placebo and were primarily mild-to-moderate in severity. Application-site erythema was the most common reaction (5%). Further, most patients in both treatment groups had a skin reaction score of 0 (no evidence of irritation) on both axillae at baseline, day 15 and day 29, showing a similar local tolerability between the treatment groups.[24]

Table 18: Adverse drug reactions by system organ class and preferred term (SAFa, N=171)

	Number (%)[a] of patients			
System organ class (MedDRA)	GPB 1% cream		Placebo	
Preferred term	(N=87)		(N=84)	
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]

Vertigo	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]	[redacted]	[redacted]
Eye irritation	[redacted]	[redacted]	[redacted]	[redacted]
Ocular hyperemia	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Application site dermatitis	[redacted]	[redacted]	[redacted]	[redacted]
Application site erythema	[redacted]	[redacted]	[redacted]	[redacted]
Application site pain	[redacted]	[redacted]	[redacted]	[redacted]
Application site papules	[redacted]	[redacted]	[redacted]	[redacted]
Application site pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Application site folliculitis	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Nasal dryness	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 57 of the CSR[29]
Only TEAEs with possible, probable or definite relationship, or missing relationship assessment are displayed. N = 0 is shown as '-'. a Percentages are based on the total number of patients per treatment group.
Abbreviations: GPB, glycopyrronium bromide; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; SAFa, safety analysis set (Phase 3a); TEAE, treatment-emergent adverse event.

2.6.2 Hyp1-18/2016 Phase 3b

2.6.2.1 Compliance

During the first 4 weeks of treatment, overall, 66.2% of patients treated with GPB 1% cream were at least 75% compliant and 83.1% of patients were at least 50% compliant. After Week 4 of the Phase 3b part, over 70% of patients were compliant (i.e., those patients who applied the cream at least twice a week) until Week 52, and 66% of patients were compliant between Week 52 and Week 72. Based on diary entries, the median number of applications per patient per week decreased as expected after Week 4 when the IMP was applied as needed ranging from 3.0 to 5.0 applications per patient per week up until Week 72.[29]

2.6.2.2 Discontinuations

20 patients prematurely discontinued the study due to 33 TEAEs, 3 of which were serious but unrelated, and 24 of which were classified as ADRs.[25]

2.6.2.3 Adverse events

For safety measurement, the frequency and severity of AEs, SAEs and TEAEs were analysed. Investigators used a skin reaction score to assess local tolerability at the application sites. Treatment period was 72 weeks and safety, and tolerability follow-up were observed 4 weeks after end of treatment, that is at week 76.

Overall, 463 ADRs (i.e. TEAEs with possible, probable, or certain relationship to the IMP, or missing relationship assessment) were reported in 170 patients (out of 518; 33.0%) treated with GPB 1% cream between Baseline and Week 72). Accordingly, 67% of patients did not exhibit any ADR during the studied period. Most patients with ADRs had recovered or were recovering at study completion. 23 patients had 28 serious TEAEs, two of which (mydriasis and unequal pupils) qualified as suspected unexpected serious adverse reactions (SUSARs). For the unequal pupils, the treatment with GPB 1% cream was interrupted until the event had resolved 1 day after onset. No action with GPB 1% cream was taken for the mydriasis and the event resolved 2 days after onset. All other serious TEAEs were assessed as unlikely or not related to GPB 1% cream. Most reported TEAEs were mild or moderate. Of all ADRs that occurred in more than two patients, dry mouth was the most common ADR in 62 of 518 of patients (12%) even though lower percentage of patients reported a dry mouth from week 4 to 72 (5.8%) compared to baseline to week 4 (9.8%). Topical application of GPB 1% cream was overall well-tolerated with erythema in 37 of 518 patients (7.1%) and pruritus in 18 of 518 patients (3.5%) being the most frequent at the application site ADRs. Other ADRs occurred in 3.3% of the patients or less and included dry eye, nasal dryness, visual impairment, and headache. All ADRs were of mild to moderate severity, were reversible after application was paused, however 14 patients discontinued the study due to ADRs.[29]

Table 19: Adverse drug reactions by system organ class and preferred term reported in ≥1% of patients in any treatment period (SAFb, N = 518)

	Number (%)[a] of patients					
System organ class (MedDRA)	BL to Day 29/Week 4		Day 29/Week 4 to Week 72		BL to Week 72	
Preferred term	(N = 438)[b]		(N=518)		(N=518)[c]	
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and adm. site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Application site dermatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Application site eczema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Application site erythema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Application site irritation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Application site pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Application site papules	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Application site pruritus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Application site rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Application site folliculitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean cell volume increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Nasal dryness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CSR[29]
Each patient is counted at most once for the line total. N = 0 is shown as '-'. Only TEAEs with possible, probable, or certain relationship to GBP 1% cream or with missing relationship are displayed.[a] Percentages are based on the number of patients in each treatment period.[b] Patients receiving placebo in the Phase 3a part are not included.[c] Only TEAEs experienced under treatment with 1% GPB cream are included.
Abbreviations: Adm, administration; BL, baseline; GPB, glycopyrronium bromide; MedDRA, medical dictionary for regulatory activities; N = number of patients; SAFb, safety analysis set (Phase 3b); TEAE, treatment-emergent adverse event.

2.7 Ongoing Studies

No ongoing studies.

2.8 Interpretation of clinical effectiveness and safety evidence

Summary

- GPB 1% cream is generally well tolerated, and the majority of patients remained on treatment throughout the clinical study
- Dry mouth is the only anticholinergic adverse drug reaction with GPB 1% cream that is reported in over 10% of patients after 4 weeks of once-daily treatment (median of 7 applications per week). In the long-term study a lower percentage of patients reported a dry mouth from week 4 to 72 (5.8%) compared to baseline to week 4 (9.8%).

2.8.1 Principal findings

The clinical development programme demonstrated the efficacy and safety of GPB 1% cream for treating severe PAHH. Importantly, efficacy was demonstrated through the objective measure of reduction of sweat volume through gravimetric measurement, and through patient reported measurements using three widely used and validated instruments, HDSS, DLQI and HidroQoL. Treatment was well tolerated, with mostly mild to moderate adverse effects and low numbers of patients stopping treatment. GPB 1% cream is a suitable long-term treatment for PAHH.

2.8.1.1 Strengths of the evidence base

Efficacy and safety have been demonstrated versus placebo. The sponsor had no knowledge of any placebo-controlled efficacy study for severe hyperhidrosis extending a 4-week comparison of active treatment and placebo treatment. The gravimetric measurement after 4 weeks is a standard objective endpoint for the development of medicinal products

intended for the treatment of hyperhidrosis. In the Phase 3a placebo controlled part of the study,[24] daily application of GPB 1% cream for four weeks significantly reduced sweat production ($p = 0.004$) and improved QOL compared to placebo.

The phase 3b study[25] is the longest and largest prospective PAHH study with a topical anticholinergic agent, providing confidence in the long-term suitability of GPB 1% cream for the treatment of PAHH, which is key given this is generally a life-long condition. At 12 weeks, sweat production had a median reduction of 66% ($p < 0.0001$) despite reduced application frequency after week 4. Over 72 weeks efficacy and improvements in quality of life were maintained despite further reduction in the application frequency after 12 weeks. The prospective 72-week long-term study is longer than prospective open label studies conducted with BTX or oral anticholinergics.

2.8.1.2 Potential limitations of the evidence base

In the UK treatment pathway for PAHH, patients will typically have tried an aluminium antiperspirant as first line therapy. In the phase 3b study, 52 out of 357 newly recruited patients had recorded a previous treatment for hyperhidrosis, which mainly included the use of deodorants and antiperspirants.[25] Patients could however, only enter the study if their hyperhidrosis was severe according to HDSS, and these are the patients for whom first line therapy is likely to prove inadequate. In addition, patients in the UK who find effective relief from aluminium antiperspirants and can persist with treatment, will not progress to GPB 1% cream.

2.8.2 Generalisability of the study population

Patients who do not achieve satisfactory results with highly concentrated antiperspirants often have a severe form of the condition and actively seek medical intervention for more effective treatment options. GPB 1% cream is an ideal option for those patients especially since most other options are either not licensed or more invasive and require referral and/or administration in secondary care.

Analysing all parameters that define the study population (in- and exclusion parameters, application mode, efficacy parameters; tables above) the sponsor is convinced that study population (defined by in- and exclusion criteria) corresponds well to the real world PAHH patient population and that study parameters (efficacy parameters like sweat reduction or QoL) are relevant in real-world clinical practice and for real-world patients.

3 Cost effectiveness

3.1 Published cost-effectiveness studies

An SLR has been conducted, with searches run 25 March 2025, to identify economic evaluations in the management of adult patients with HH from the published literature, including HTA documents. A detailed description of the search methodology, a PRISMA flow diagram, and results are presented in Appendix E.

In total, four studies across six publications were identified in the SLR. Table 20 summarises each of the identified studies. Of the four identified studies, three modelled treatment effectiveness using a ≥2-point improvement in HDSS score, while one used the Dermatology Life Quality Index (DLQI). Two models were based on single-centre pre- and post-treatment analyses, whereas the other two used data sourced from published literature. Two studies reported outcomes in terms of incremental cost per additional QALY gained (Bloudek et al. (2021) and Wade et al. (2017)).[18,39,40] Whereas, Gibbons et al. (2015) reported a cost-comparison and Isla-Tejera et al. (2013) reported cost per additional responder.[41–43]

Both Bloudek et al. (2021) and Wade et al. (2017) employed state transition models. The model in Bloudek et a. (2021), developed in Excel, compared glycopyrronium tosylate with topical aluminium chloride in patients with PAHH. The model in Wade et al. (2017), developed in R, evaluated sequences of treatments for patients with HH.

Key assumptions relevant to this appraisal include:

- **Annual frequency of botulinum toxin treatment:** Bloudek et al. (2021) and Wade et al. (2017) assumed two procedures per year, Gibbons et al. (2015) assumed 2.1, and Isla-Tejera et al. (2013) allowed a maximum of two.
- **Treatment discontinuation:** Bloudek et al. (2021) assumed that patients reverted to their baseline HDSS score after discontinuing treatment.
- **Oral antimuscarinic comparators:** Wade et al. (2017) included propantheline bromide, oxybutynin, and oral glycopyrronium bromide, assuming equal efficacy across these.
- **Utilities:** Utilities were only included in two of the four studies. Both Bloudek et al. (2021) and Wade et al. (2017) derived utility values from Kamudoni et al. (2014),[44] assuming patients with an HDSS score of 1 have utility equivalent to that of the general population.

Table 20: Summary list of published economic models[18,39–43]

Study	Analysis	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Bloudek et al. (2021)	CEA	Perspective: US Intervention: glycopyrronium tosylate Comparator: Topical aluminium chloride Model structure: Response-based HDSS state transition model. Responder ≥2 HDSS improvement. Built in Excel. Time horizon: 5 years	1st line PAHH	Glycopyrronium tosylate: 3.75 Topical aluminium chloride: 3.63	Costs in USD Glycopyrronium tosylate Initial treatment: $10,976 Subsequent treatment: $1,771 (botulinum toxin: $774, microwave thermolysis: $758, oral anticholinergics: $14, local excision: $176, endoscopic thoracic sympathectomy: $50) Total: $12,747 Topical aluminium chloride Initial treatment: $17	Cost/QALY: $87,238

					Subsequent treatment: $2,147 (botulinum toxin: $1,001, microwave thermolysis: $866, oral anticholinergics: $17, local excision: $206, endoscopic thoracic sympathectomy: $58) Total: $2,164	
Wade et al. (2017) (full publication) Rice et al. (2017) (abstract)	CEA	Perspective: UK Sequences: Iontophoresis sponge (I) I > curettage (C) > endoscopic thoracic sympathectomy (E) (ICE) I > botulinum toxin (B) > medication (M) > C > E (IBMCE) B>M>I>C>E (BMICE)	Severe PAHH	I: 18.47 ICE: 19.30 IBMCE: 19.84 BMICE: 19.85 MBICE: 19.85	Mean cost, GBP, I: £900 ICE: £1,121 IBMCE: £6,091 BMICE: £7,468 MBICE: £8,195	ICER, vs. I: ICE: £253 IBMCE: £9,304 BMICE: £137,046 MBICE: £1,407,569

		M>B>I>C>E (MBICE) Model structure: Response-based HDSS sequencing state transition model. Responder ≥2 HDSS improvement. Built in R Time horizon: 48 years				
Gibbons et al. (2016)	Single centre CCA	Perspective: Ireland Intervention: Botulinum toxin Comparator: Endoscopic thoracic sympathectomy Model structure: Pre- and post-treatment. Response based on DLQI.	AHH	NA	Mean cost of ETS, Euros 1,390	NA

		Time horizon: 4-6 weeks following treatment				
Isla-Tejera et al. (2013) (full publication) Alvarez et al. (2013) (abstract)	CEA	Perspective: Spain Intervention: Botulinum toxin Comparator: Endoscopic thoracic sympathectomy Model structure: Pre- and post-treatment. Effectiveness based on HDSS. Responder ≥2 HDSS improvement. Time horizon: 1 year	Palmer HH	Incremental effectiveness (responder): 0.24	Total costs, 5 year period: Botulinum toxin €178,704 Endoscopic thoracic sympathectomy €144,896	ICER, cost/additional responder in the first year: €125

Abbreviations: AHH, axillary hyperhidrosis; BMICE, botulinum toxin > medication > iontophoresis > curettage > endoscopic thoracic sympathectomy; CEA, cost-effectiveness analysis; CEM, cost-effectiveness model; DLQI, Dermatology Life Quality Index; E, endoscopic thoracic sympathectomy, ETS, endoscopic thoracic sympathectomy; GBP, British Pound Sterling, HDSS, Hyperhidrosis Disease Severity Scale, I, iontophoresis; ICER, incremental cost-effectiveness ratio; ICE, iontophoresis > curettage > endoscopic thoracic sympathectomy; IBMCE, iontophoresis > botulinum toxin > medication > curettage > endoscopic thoracic sympathectomy; MBICE, medication > botulinum toxin > iontophoresis > curettage > endoscopic thoracic sympathectomy; M, medication (e.g., antimuscarinics); NA, not available / not applicable; PAHH, primary axillary hyperhidrosis; QALY, quality-adjusted life year; USD, United States Dollar

3.2 Economic analysis

The economic SLR identified four economic models evaluating either the cost-effectiveness or cost comparison of treatments in the HH setting. While insights from these published models have informed the current appraisal, none were publicly available or directly suitable for this submission. For instance, of the two more comprehensive state transition models, one was developed from a US healthcare perspective and does not align with the UK treatment pathway. The other, although UK-based, focused on a broader HH population, emphasised secondary care (despite the increasing shift toward primary care), and was considered overly complex relative to the available data - using a sequencing model built in R. As such, although the literature is referenced throughout the submission, a de novo economic model has been developed specifically for this appraisal, with assumptions informed and supported by the identified studies.

3.2.1 Patient population

In line with the NICE final scope and the UK marketing authorisation (Section 2), the population considered in the economic model is adults with severe PAHH.

The model includes age, gender, and HDSS score as baseline characteristics. In the base case, these are derived from the FAS population of the Phase 3b clinical trial (FASb), consistent with the source of efficacy data for GPB 1% cream - Table 21 and Table 22, respectively. Scenario analyses explore the impact of using baseline age and gender from the PPS population of the Phase 3b trial (PPSb) and the FAS population of the Phase 3a trial (FASa).

Table 21: Baseline characteristics (age and gender)

	Mean	SD	N
Baseline age			
FASb	35.6	11.8	518
PPSb	[redacted]	[redacted]	[redacted]
FASa	[redacted]	[redacted]	[redacted]
Proportion female			
	n	N	%
FASb	274	518	52.9%
PPSb	[redacted]	[redacted]	[redacted]
FASa	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; N, number; PPS, per-protocol set; SD, standard deviation

Source: Table 9, Table 10, PostHoc Table 2_b, CSR[29]

Table 22: Baseline HDSS distribution (FASb)

	Baseline, N	Baseline, %
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Scale; N, number
Source: Table 4.2.1_b, CSR[29]

3.2.2 Model structure

The economic model has been developed with a Markov state transition model structure based on HDSS status in Microsoft Excel (Version 2502).

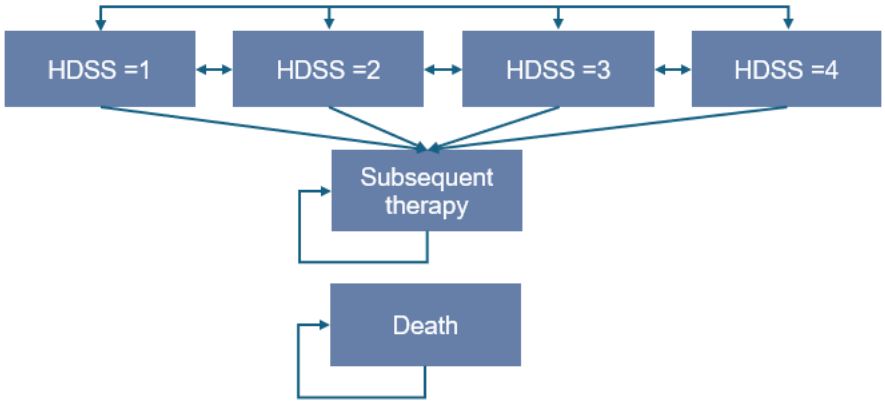
This model structure was chosen because it reflects the transitions relevant to patients with PAHH. Feedback from a UK clinical expert highlighted that assessments such as gravimetric measurement are not used in clinical practice and that response is assessed based on patients' perceived symptom severity.[12] The HDSS is a patient-reported outcome measure that is used to assess the severity of daily sweating and its impact on daily activities. Therefore, the HDSS-based structure reflects outcomes which matter to patients and aligns with the assessment of response in UK clinical practice.

Transitions between health states can occur over time due to treatment responses, or loss of response. The state transition model is particularly suited to this context, as it allows use of available data, which is reported at discrete time points, to model transitions between health states over time. Furthermore, it is well-suited for chronic conditions like PAHH, enabling the use of short-term clinical study data and allowing for the extrapolation of these data into long-term outcomes.

The Markov state transition structure based on HDSS health states is also consistent with three of the four economic models identified in the SLR (Section 3.1).

In summary, the HDSS-based Markov state transition model captures outcomes that are meaningful to patients, aligned with UK clinical practice, consistent with the clinical trial data, appropriate for extrapolating short-term results to long-term outcomes, and supported by published literature. The model structure is depicted in Figure 9.

Figure 9: Model structure



Abbreviations: HDSS, Hyperhidrosis Disease Severity Scale

Transitions between HDSS health states for GPB 1% cream are informed by data from the Phase 3b clinical trial. For comparator treatments, transition probabilities are estimated using odds ratios (ORs) from indirect treatment comparisons (ITCs) based on published literature (Section 2.9). While on treatment, patients can transition between relevant HDSS health states. Upon discontinuation, they move to a subsequent therapy health state, where they receive a weighted mix of subsequent therapies and are assumed to revert to their baseline HDSS levels. This assumption aligns with Bloudek et al. (2021).[39]

The Phase 3b clinical data are used for GPB 1% cream, rather than the Phase 3a clinical data, as this trial has data up to 72-weeks. Whereas the Phase 3a clinical data are only up to 4-weeks. However, the Phase 3a clinical data are randomised and placebo-controlled. Therefore, these data inform the ITCs for GPB 1% cream vs. placebo.

No excess mortality is anticipated from PAHH. Therefore, transitions to the death health state are informed by age- and gender-adjusted background mortality sourced from the England and Wales lifetables (2021-2023).[45] Costs and QALYs are accrued according to the proportion of patients in the HDSS health states over time.

The cycle length in the economic model is 2-weeks – aligning with the timepoints for which the impact on HDSS is reported in the Phase 3b clinical trial for GPB 1% cream. A half cycle correction is applied using the life table method to account for uncertainty in the timing of transitions within the cycle period, where the time in each cycle is estimated by taking the average of the number of people at the start and end of the cycle. A scenario analysis explores the impact of excluding the half-cycle correction.

In accordance with the NICE methods and process guide, a lifetime horizon (65 years) is adopted.[46] The lifetime horizon reflects the differential long-term outcomes experienced by patients treated with GPB 1% cream. After 65 years, 99.1% of patients are predicted to have died across all treatment arms. Alternative time horizons (20, 40, and 60 years) are explored in scenario analyses.

The analysis is conducted from the perspective of the National Health Service (NHS) and personal social services (PSS) in England and Wales, and costs and health outcomes are discounted at an annual rate of 3.5%. Table 23 outlines the key features of the economic

analysis. As there are no published NICE appraisals for HH, direct comparisons with previous appraisals are not available.

Table 23: Features of the economic analysis

Factor	Current evaluation, chosen values	Current evaluation, justification
Time horizon	65 years	A lifetime horizon was selected, as per the NICE reference case to capture all relevant differences in costs and outcomes.[46] A lifetime horizon of 65 years is assumed. Scenario analyses explored 20, 40, and 60 years.
Treatment waning effect?	No	No treatment waning is assumed for GPB 1% cream. For patients who remain on treatment beyond the 72-week Phase 3b trial period, the model conservatively assumes no further movement between HDSS health states. While some individuals may experience a reduction in treatment effect over time, this is offset by the larger proportion of patients who continue to improve, as evidenced by an increase in those achieving ≥2-point improvements in HDSS scores between weeks 52 and 72 in the FASb population, and by the ongoing reduction in mean HDSS scores reported in Szeimies et al. (2022).[25] Therefore, the base case assumption is conservative as the overall HDSS change over time would likely be positive. A scenario analysis explores the potential impact of continued improvement beyond 72 weeks, based on these observed trends. In line with assumptions for GPB 1% cream, and due to the absence of long-term data for antimuscarinics in the severe PAHH population, the model also assumes no further change in HDSS health states for patients continuing treatment with oral antimuscarinics after 72 weeks. For botulinum toxin, waning is well-established and requires repeated administrations. Its treatment effect is modelled based on peak efficacy at 4 weeks, followed by a decline to no effect by 6 months, at which point patients are assumed to return to baseline HDSS values. These timepoints (4 weeks and 6 months) are explored in scenario analyses.

Source of utilities	Kamudoni et al. (2014)[44]	Utilities are sourced from the literature. Kamudoni et al. (2014) report EQ-5D utility values by health state.
Source of costs	British National Formulary (BNF) accessed May 2025, NHS Reference Costs 2023/24, and the PSSRU 2024[47–49]	As per the NICE reference case.

Abbreviations: EQ-5D, EuroQol- 5 Dimension; GPB, glycopyrronium bromide; HDSS, hyperhidrosis disease severity scale; NHS, National health service; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit.

3.2.3 Intervention technology and comparators

3.2.3.1 Intervention

The intervention in the economic model is glycopyrronium bromide (GPB) 1% cream, aligned with the anticipated UK marketing authorisation, the EU SmPC, and the NICE final scope.[50,51] The prescribed dose is 0.54g per axilla, totalling 1.08g per application. It is recommended that patients apply 1% GPB 1% cream to both axillae once daily for the first 4 weeks. From week 5, applications can be made anywhere from twice a week to daily, depending on individual patient needs.

The model accounts for dose variation and compliance within each application by comparing the mean grams used in the first 29 days of treatment ([redacted]) to the expected dose outlined in the protocol (1.08g x 29 = 31.3g), from the Phase 3b clinical trial.[29] These data indicate that patients used, on average, [redacted] of the anticipated dose. Although patients are using a lower dose than indicated in the SmPC, there is no associated product wastage, as GPB 1% cream has a long shelf life and can be retained for future use in subsequent applications.

After 4 weeks in the Phase 3b clinical trial, patients were allowed to apply GPB 1% cream between twice weekly and daily, depending on individual needs - an approach reflective of real-world clinical practice. To align with this variability and maintain consistency with the observed efficacy outcomes, the model uses the mean number of applications recorded in the trial to represent treatment use (Table 24). These application frequencies correspond directly to the efficacy data used to inform the base case for GPB 1% cream in the model. Beyond 72 weeks, the model assumes the mean number of applications at 72 weeks for the rest of the model time horizon.

Table 24: Mean number of applications of GPB 1% cream per week in the Phase 3b clinical trial

Week	N	Mean/week	SD
2	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]

18	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]
34	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]
38	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]
44	[redacted]	[redacted]	[redacted]
46	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]
52	[redacted]	[redacted]	[redacted]
54	[redacted]	[redacted]	[redacted]
56	[redacted]	[redacted]	[redacted]
58	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]
62	[redacted]	[redacted]	[redacted]
64	[redacted]	[redacted]	[redacted]
66	[redacted]	[redacted]	[redacted]
68	[redacted]	[redacted]	[redacted]
70	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; N, number of patients; SD, standard deviation
Source: Table 5.4.2_b, CSR[29]

3.2.3.2 Comparators

In line with the NICE final scope, the economic model includes oral antimuscarinics (propantheline bromide, off-label oxybutynin, and off-label oral GPB) and botulinum toxin injection as comparators.[50] As outlined in Section 2, the treatment landscape for severe PAHH in the UK involves a combination of oral antimuscarinics and botulinum toxin.

The economic model adopts a weighted basket approach for the oral antimuscarinics comparator, based on the assumed similar outcomes. This includes the costs of propantheline bromide, oxybutynin, and oral GPB, with the weighted average reflecting their relative usage. This approach aligns with assumptions made in the literature.

Table 25 shows the distribution of therapies included in the oral antimuscarinics comparator and the dosing information sourced from the British National Formulary (BNF)[52] and the NICE Evidence Summary for oral GPB.[18] The distribution is based on a UK survey of dermatologists reported in Wade et al. (2017), and the dosing schedules shown are consistent with the findings of that survey. While the base case assumes a daily dose of 7.5 mg for oxybutynin, based on the Schollhammer et al. (2015) study used in the ITC, a scenario analysis assesses the impact of a higher dose of 12.5 mg/day. This alternative reflects the assumptions used in the economic model by Wade et al. (2017) and corresponds to the midpoint of the dosing range reported in the survey of UK dermatologists.

In the absence of data, 100% dose intensity is assumed for oral antimuscarinics. A scenario analysis explores the impact of the same dose intensity as GPB 1% cream.

Table 25: Distribution and doses associated with oral antimuscarinics

	Proportion	Dose
Propantheline bromide	35.4%	15 mg 3 times a day and 30mg before bed (75mg/day)
Oxybutynin	46.2%	2.5 mg 3 times a day (7.5mg/day)
Oral GPB	18.5%	2 mg once a day

Abbreviations: GPB, glycopyrronium bromide; mg, miligram.

As outlined in Section 2, access to botulinum toxin treatment varies widely across NHS Trusts and clinics and is expected to decline further due to ongoing efforts to transition the management of PAHH to primary care settings. Additionally, increasing secondary care waiting times and the risk of patients being lost in the referral system further reduce accessibility. Although botulinum toxin is included as a comparator in the economic model, its relevance in current clinical practice is limited and continues to decline. This is supported by the 2019 Hyperhidrosis UK patient leaflet, which notes that the treatment is predominantly accessed privately, with only a small number of NHS clinics funded to provide it. Furthermore, the treatment effects are short-lived (typically lasting three to six months) and require repeated administration, making it unsuitable for many patients.[19] These

observations are consistent with feedback received from UK clinical experts, both during the company's consultations and from the two clinicians and the Hyperhidrosis UK representative who participated in the scoping workshop for this appraisal.[12]

The economic model assumes the use of 50U of botulinum toxin per axilla (100U in total), consistent with the SmPC for Botox, UK clinical expert input, and the clinical trial data used to inform efficacy in the base case.[12,14,27] Scenario analyses explore the impact of 75U per axilla (150U) and an average across 50U and 75U doses, varying the doses and the source of efficacy and safety data accordingly.

It is further assumed that patients will require two treatment sessions per year. This is supported by clinical feedback and efficacy data for botulinum toxin informing the base case, which indicate a treatment effect of 201 days. This assumption is also aligned with previously published economic models (Appendix E): Alvarez et al. (2013), Isla-Tejera et al. (2013), Bloudek et al. (2021), and Wade et al. (2017) all assumed two sessions per year; and Gibbons et al. (2015) assumed 2.1 sessions annually.[18,39,42,43] A scenario analysis assesses the impact of assuming 1.8 treatment sessions per year, based on the need for re-treatment following the end of the treatment effect at 201 days (201/365.25) reported in Lowe et al. (2007).

3.3 Clinical parameters and variables

3.3.1 GPB 1% cream

As described in Section 3.2.2, transitions between HDSS health states for GPB 1% cream are based on the Phase 3b clinical trial for GPB 1% cream.

Table 26 presents the number of patients who were HDSS responders with ≥2 points improvement from baseline, the number of patients who were HDSS responders with ≥1 points improvement from baseline, and the number of patients who had an improvement in HDSS of 1 or 2 points from baseline from the FASb population at weeks 4, 8, 12, 28, 52, and 72 (N=518).

In the PPSb population, [redacted] patients were excluded for reasons such as early termination ([redacted]), time window violation ([redacted]), product use ([redacted]), antiperspirant use ([redacted]), violated exclusion criteria ([redacted]), forbidden medication ([redacted]), violated IC ([redacted]), and gravimetric assessment ([redacted]). Therefore, the PPSb population comprised [redacted] patients. 29

Table 27 presents the number of patients who were HDSS responders with ≥2 points improvement from baseline from the PPSb population at weeks 12 and 28 (N=[redacted]).

In the base case, the economic model uses data from the FASb population as this reflects the more comprehensive data set and is aligned with how patients would likely use GPB 1% cream in clinical practice. The data from the PPSb population are used in a scenario analysis, with a multiplier reflecting the proportional improvement in the PPSb population compared to the FASb population for the ≥2 points improvement from baseline endpoint, applied to the ≥1 and 1-2 points improvement from baseline endpoints.

Table 26: Patients with improvement in HDSS in the Phase 3b (FASb)

Week	>=2			>=1			1 or 2		
	n	N	%	n	N	%	n	N	%
4	[redacted]								
8	[redacted]								
12	[redacted]								
28	[redacted]								
52	[redacted]								
72	[redacted]								

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Scale; N, number of patients.
Source: Table 41, Table 4.3.4_b, Table 4.4.3_b, and Table 6_b, CSR[29]

Table 27: Patients with improvement in HDSS in the Phase 3b (PPSb)

Week	>=2		
	n	N	%
12	[redacted]		
28	[redacted]		

Abbreviations: HDSS, Hyperhidrosis Disease Severity Scale; N, number of patients; PPS, per protocol set
Source: Table 24, Table 25, CSR[29]

Transition probability matrices are estimated to describe the transitions of patients receiving GPB 1% cream from baseline to week 4, 8, 12, 28, 52, and 72. At each timepoint the probability of achieving a 1, 2, or 3 point improvement in HDSS score is calculated from the data. Table 28 describes the transition probability matrices applied at the relevant time points relative to baseline in the economic model.

The probability of improvements in HDSS score is assumed to be constant across HDSS health states. For example, the [redacted]% improvement in HDSS score observed from baseline to week 4 is applied uniformly to all patients, regardless of their starting health state. This means that patients in HDSS 2, HDSS 3, and HDSS 4 all have a [redacted]% chance of experiencing a 1-point improvement.

The economic model uses a 2-week cycle length. Therefore, whilst the transition probabilities inform the distribution across the HDSS health states at weeks 4, 8, 12, 28, 52, and 72, the distribution at each 2-week interval for which observed data are unavailable, is estimated based on a step increment calculated from the data points that are available.

Table 28: Base case transition probability matrices, trial period | GPB 1% cream

		HDSS health state (moving to)				Sum
		1	2	3	4	
Baseline to week 4						
HDSS health state (moving from)	1	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
	2	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
	3	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
	4	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
Baseline to week 8						
HDSS health state (moving from)	1	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
	2	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
	3	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
	4	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
Baseline to week 12						
HDSS health state (moving from)	1	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
	2	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
	3	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
	4	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
Baseline to week 28						
HDSS health state (moving from)	1	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
	2	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
	3	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
	4	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
Baseline to week 52						
HDSS health state (moving from)	1	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
	2	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
	3	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
	4	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*

Baseline to week 72						
HDSS health state (moving from)	1	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
	2	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
	3	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*
	4	[redacted]	[redacted]	[redacted]	[redacted]	*100.0%*

Abbreviations: GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale.

For patients who continue treatment beyond the 72 week Phase 3b trial period, the model conservatively assumes no further transition between HDSS health states. Although some individuals may experience a decline in treatment effect over time, this is outweighed by the greater proportion of patients who continue to show improvement. This is supported by the increase in the proportion of patients achieving a ≥2-point improvement in HDSS scores from [redacted] % at week 52 to [redacted] % at week 72 in the FASb population, as well as the continued reduction in mean HDSS scores reported by Szeimies et al. (2022).[25] Therefore, the base case assumption is conservative, as the overall HDSS trajectory over time is likely to be positive. A scenario analysis evaluates the potential impact of ongoing improvement beyond 72 weeks, applying a [redacted] % probability of improvement in each 2-week model cycle based on observed changes between weeks 52 and 72.

Table 29 presents the transition probability matrix applied beyond the 72 week trial period each model cycle.

Table 29: Base case transition probability matrices, beyond the trial period | GPB 1% cream

		Week 72+				
HDSS health state (moving from)	1	100.0%	0.0%	0.0%	0.0%	*100.0%*
	2	0.0%	100.0%	0.0%	0.0%	*100.0%*
	3	0.0%	0.0%	100.0%	0.0%	*100.0%*
	4	0.0%	0.0%	0.0%	100.0%	*100.0%*

Abbreviations: HDSS, Hyperhidrosis Disease Severity Scale.

These transition probabilities are applied to all patients receiving GPB 1% cream within the economic model. Following discontinuation of GPB 1% cream, it is assumed that patients will revert to their original HDSS health state. Treatment duration and discontinuation is discussed in Section 3.3.3.

3.3.2 Comparative efficacy

Comparative efficacy between GPB 1% cream and relevant comparators is estimated using Bucher ITCs anchored through a placebo arm (Section 2.9).

Table 30 presents the ORs applied in the base case for antimuscarinics vs. GPB 1% cream for the ≥2 HDSS improvement and ≥1 HDSS improvement endpoints and for botulinum vs. GPB 1% cream for the ≥2 HDSS improvement endpoint. Scenario analyses explore the use of the PPSa data for GPB 1% cream vs. placebo, comparator data from the NMA published in Wade et al. (2017), and differential efficacy associated with a second session of botulinum toxin.

Table 30: ORs applied in the base case to inform relative efficacy[26,27,29]

Treatment	Population	Timepoint	Endpoint	OR
GPB 1% cream	FASa	Day 29	≥2	
Antimuscarinics	Schollhammer et al. (2015)	6 weeks	≥2	[redacted]
GPB 1% cream	FASa	Day 29	≥1	
Antimuscarinics	Schollhammer et al. (2015)	6 weeks	≥1	[redacted]
GPB 1% cream	FASa	Day 29	≥2	
Botulinum toxin 100U	Lowe et al. (2007)	4 weeks after initial tx	≥2	[redacted]

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; OR, odds ratio; U, unit.

3.3.2.1 Antimuscarinics

The economic model reflects the comparative effectiveness of antimuscarinics vs. GPB 1% cream by multiplying the ORs for the ≥1 or ≥2 HDSS improvement endpoints by the GPB 1% cream data at weeks 4, 8, 12, 28, 52, and 72, matching the time points at which GPB 1% cream data are available from FASb. As data are unavailable for 1-2 HDSS improvement for antimuscarinics, the OR for the ≥1 HDSS improvement endpoint is assumed.

In the scenario where the PPSb data are used for GPB 1% cream, ORs for antimuscarinics vs. GPB 1% cream are re-calculated based on these data and applied to weeks 12 and 28, matching the time points at which GPB 1% cream data are available from PPSb.

In line with assumptions for GPB 1% cream, and due to the absence of long-term data for antimuscarinics in the severe PAHH population, the model assumes no further change in HDSS health states for patients continuing treatment with oral antimuscarinics after 72 weeks.

Clinical expert input indicates that antimuscarinics are rarely used for long-term maintenance due to their adverse event (AE) profile and a diminishing benefit-risk balance over time. Instead, they are typically prescribed as "on-demand" treatments.[12] This perspective is supported by feedback reported in Wade et al. (2017), which noted that oral medications were considered to offer limited effectiveness and were associated with troublesome side

effects. As a result, patients are often advised to use these medications only when needed (such as for social or public events) rather than on a continuous daily basis.[18] Therefore, it is important to distinguish between: patients who remain on antimuscarinics and maintain effectiveness over time, which the model captures through these transitions, and patients who discontinue treatment, who are assumed to lose all therapeutic benefit and return to their baseline HDSS state. Treatment duration and discontinuation is discussed in Section 3.3.3.

3.3.2.2 Botulinum toxin

The economic model reflects the comparative effectiveness of botulinum toxin vs. GPB 1% cream by multiplying the ORs for the ≥2 HDSS improvement endpoint by the GPB 1% cream data at weeks 4, 8, 12, 28, 52, and 72, matching the time points at which GPB 1% cream data are available from FASb. As data are unavailable for the ≥1 and 1-2 HDSS improvement endpoints for botulinum toxin, the proportional difference between ≥1 and ≥2 HDSS improvement ORs estimated for antimuscarinics is used to estimate the OR for the ≥1 and 1-2 HDSS improvement endpoints for botulinum toxin. A scenario analysis explores the use of the ≥2 HDSS improvement OR across all endpoints for botulinum toxin vs. GPB 1% cream. However, the data from the Phase 3a GPB 1% cream clinical trial and Schollhammer et al. (2015) indicate that the response rates for a ≥1 HDSS improvement are much less than the ≥2 HDSS improvement – supporting the base case assumption.

In the base case, the data for botulinum toxin come from the 50U per axilla (100U) dose data reported in Schollhammer et al. (2015) for the first botulinum toxin treatment. Scenario analyses explore the data from the 75U per axilla (150U) dose data and the combined botulinum toxin doses, varying the doses and the source of safety data accordingly. In the scenario where the PPSb data are used for GPB 1% cream, ORs for botulinum toxin vs. GPB 1% cream are re-calculated based on these data and applied to weeks 12 and 28, as these are the only time points at which GPB 1% cream data are available.

Because botulinum toxin has a well-documented waning effect, where treatment efficacy peaks and then gradually declines until symptoms return to baseline, the model incorporates two key parameters to represent this pattern:

1. Time to maximum efficacy. The base case assumes 4 weeks.
2. Frequency of treatment per year. The base case assumes two botulinum toxin treatments annually, consistent with clinical feedback from UK practice.

It is assumed that each new botulinum toxin treatment is administered once the patient's HDSS score has returned to baseline, marking the end of the treatment effect from the previous session. Therefore, in the base case, the maximum treatment effect is reached at week 4, as defined by the OR for botulinum toxin (applied relative to GPB 1% cream), and then wanes linearly from week 4 to month 6. At that point, the patient receives the next scheduled botulinum toxin treatment. Scenario analyses are conducted to test the impact of the different assumptions, including maximum efficacy occurring at 8 or 12 weeks, and reduced treatment frequency, assuming 1.8 botulinum toxin treatments per year.

In the base case, it is assumed that the efficacy associated with subsequent botulinum toxin treatment is aligned with the initial treatment. There is currently inconclusive evidence in the literature regarding whether the treatment effect of botulinum toxin changes with subsequent sessions for HH. Some studies, such as Lowe et al. (2007), suggest that treatment effectiveness may improve over time, while others indicate a potential decline in efficacy[27,53]. Whilst the treatment effect from the second botulinum toxin treatment is shown to improve in Lowe et al. (2007), the authors highlight that this may be due to the truncated follow-up and limited patient numbers receiving a second treatment. Glaser et al. (2007) present four-year longitudinal data on the efficacy of repeated botulinum toxin treatment for PAHH. While HDSS response at 4 weeks remains consistent across one to five treatment sessions, the median duration of effect steadily declines with each successive procedure.[54]

Several factors should be considered when interpreting these findings. First, patients who continue with additional botulinum toxin treatments likely represent a self-selected group who experienced a positive response to the initial treatment - this may partly explain why subsequent outcomes appear better in some cases. On the other hand, a diminishing response over time may occur in certain patients, potentially due to the development of neutralising antibodies or desensitisation of sweat glands. Patient perception also plays a role; the initial dramatic improvement can set high expectations, and when symptoms return between treatments, patients may become more aware or distressed by them - leading to a sense that follow-up treatments are less effective. Other factors that may influence the perceived or actual efficacy of subsequent treatments include variations in dosing and delays in treatment intervals (e.g., due to inconsistent scheduling or limited capacity within clinics).

Therefore, scenario analyses are conducted to explore the impact of varying treatment effectiveness in subsequent botulinum toxin sessions. We explore the use of the improved OR reported for the second session in Lowe et al. (2007), as well as scenarios assuming a 10% and 20% reduction in ORs from the initial treatment, applied to all subsequent botulinum toxin procedures.

As with GPB 1% cream and antimuscarinics, treatment discontinuation is modelled separately and patients who discontinue treatment, who are assumed to lose all therapeutic benefit and return to their baseline HDSS state. Treatment duration and discontinuation is discussed in Section 3.3.3.

3.3.3 Treatment duration

3.3.3.1 GPB 1% cream

Of the 518 patients enrolled in the Phase 3b clinical trial, 150 (29%) discontinued the study before completing the end-of-study visit. The main reasons for discontinuation were withdrawal of consent (55 patients; 10.6%), lost to follow-up (43 patients; 8.3%), other reasons (36 patients; 6.9%), and one reported death (0.2%).[25,29] Based on these data, a 2-week discontinuation probability of 0.95% for GPB 1% cream was derived and applied in each model cycle.

In the base case analysis, it is assumed that this discontinuation rate (0.95% per 2-week cycle) continues beyond the 72-week trial period and remains constant over the model time horizon. A scenario analysis is conducted to assess the impact of increasing this long-term discontinuation rate by 10% and 20%, to explore the sensitivity of the model outcomes to this assumption.

3.3.3.2 Antimuscarinics

For the treatment duration or discontinuation of oral antimuscarinics, the RCT informing the HDSS outcomes for antimuscarinics in the economic model was of a short duration (6 weeks) with no discontinuation recorded.

The NICE evidence summary on oxybutynin for HH includes two observational studies that examine the long-term use of oxybutynin in patients with HH or AHH:[55]

- Wolosker et al. (2014) conducted an RCT evaluating oxybutynin in 431 patients with AHH. By 6 months, 188 patients (50.9%) had discontinued treatment, citing reasons such as lack of improvement (n=114), loss to follow-up (n=34), good results but opted for surgery (n=26), and AEs (n=14). This study did not report on the severity or primary/secondary classification of HH.[56]
- Millán-Cayetano et al. (2017) conducted a retrospective review of 110 patients treated with oxybutynin for HH.[57] At 12 months, 38 patients (35%) had discontinued treatment, with reasons including intolerance (n=14; 13%), lack of effectiveness (n=4; 4%), both intolerance and lack of effectiveness (n=12; 11%), and patient preference (n=8; 7%). In this study, 91% had primary HH and 56% had axillary involvement.

Given that Wolosker et al. (2014) focuses specifically on AHH, it is considered more aligned with the target population for this appraisal. Therefore, the discontinuation rate of 50.9% over 6 months is used in the economic model, which translates to a 2-week discontinuation probability of 5.5%. In the base case, this rate is assumed to continue beyond the 6-month period for the full model time horizon. A scenario analysis is conducted using the discontinuation data from Millán-Cayetano et al. (2017) to assess the impact of this assumption.

3.3.3.3 Botulinum toxin

Discontinuation of botulinum toxin in the model is informed by data from Lowe et al. (2007), which reported the number of patients who discontinued after the first, second, third, and fourth procedures. The study also identified patients who did not receive a subsequent botulinum toxin treatment during the study period but had not formally discontinued. It remains unclear whether these individuals would have resumed treatment later or had permanently discontinued. Table 31 presents the number of botulinum toxin procedures recorded, the number of patients who received further treatments, those who completed the study without additional procedures, and those who formally discontinued.

Table 31: Number of botulinum toxin procedures in Lowe et al. (2007)[27]

	N	Completed study with no further treatment	Another botulinum toxin procedure	Discontinued
First procedure	214	91 (42.5%)	101 (47.2%)	22 (10.3%)
Second procedure	101	77 (76.2%)	12 (11.9%)	12 (11.9%)
Third procedure	12	9 (75.0%)	2 (16.7%)	1 (8.3%)
Fourth procedure	2	2 (100%)	0 (0%)	0 (0%)

Abbreviations: N, number of patients.

Due to limited follow-up in the study, and the fact that some patients were still at the second procedure stage when the study ended, it is assumed that data beyond the first procedure are incomplete. As such, the model uses discontinuation data from the first treatment only. In the base case, it is assumed that all patients who formally discontinued, along with half of those who completed the study without further treatment, are true discontinuers. This equates to a discontinuation proportion of 31.5%, which, based on the assumption of two treatments per year, translates into a 2 week discontinuation probability of 2.9%.

This rate is applied across the full model time horizon. To test the robustness of this assumption, scenario analyses are conducted assuming only all patients who formally discontinued and all patients who formally discontinued along with all those who completed the study without further treatment.

3.3.4 Mortality

Severe PAHH is not anticipated to impact patients' survival. Therefore, mortality rates are taken from age- and gender-adjusted England and Wales lifetables 2021-23.[45]

3.3.5 Adverse events

Adverse drug reactions (ADRs) in the Phase 3b study are defined as treatment-emergent AEs assessed as possibly, probably, or certainly related to GPB 1% cream, or where the relationship was missing. TEAEs include all AEs with an onset on or after the first application of GPB 1% cream. In the model, ADRs occurring in ≥2% of patients are considered. Additionally, any AE data reported by comparators have been extracted regardless of this threshold to allow for more complete comparisons.

AE data for oral antimuscarinics and botulinum toxin are taken from Schollhammer et al. (2015) and Lowe et al. (2007), respectively - aligning with the sources of efficacy data used in the model. Since oxybutynin is an anticholinergic and the side effect profile is well established in this drug class, it is assumed that this profile extends to other oral antimuscarinics included in the comparator arm.

In the base case, the model uses AE data from the 100U botulinum toxinrm reported in Lowe et al. (2007) aligning with the dose of botulinum toxinssumed in the base case. For scenario analyses that assess the dose and efficacy of the 150U dose or a combined estimate across both doses (Section 3.2.3.2), the corresponding safety inputs are adjusted to reflect the relevant treatment arm(s).

Table 32 presents the raw AE data for GPB 1% cream, oxybutynin, and botulinum toxin. Table 33 shows the corresponding 2-week probability of experiencing each TEAE, which is applied per model cycle for all patients remaining on treatment with GPB 1% cream, oral antimuscarinics, or botulinum toxin.

It is important to note that comparing safety across these sources is limited by differences in study duration and AE reporting. The oxybutynin data from Schollhammer et al. (2015) reflect a short-term, 6-week period and may not capture longer-term AEs, in contrast to the 52-week data for botulinum toxin, and the 72-week data available for GPB 1% cream. Additionally, the definitions and reporting of AEs vary. For example, Schollhammer et al. (2015) refer to AEs as “side effects” and only report severity for dry mouth, while Lowe et al. (2007) define AEs as treatment-related events occurring in ≥2% of patients but do not report severity.

Table 32: Observed AE data

	GPB 1% cream[29]		Antimuscarinics [26]		Botulinum toxin 100U[27]	
N	518		30		104	
Weeks	72		6		52	
	n	%	n	%	n	%
Dry eye	[redacted]	[redacted]	0	0.0%	0	0.0%
Dry mouth	[redacted]	[redacted]	13	43.3%	0	0.0%
Application site erythema/flush	[redacted]	[redacted]	1	3.3%	0	0.0%
Application site pruritus	[redacted]	[redacted]	0	0.0%	0	0.0%
Headache	[redacted]	[redacted]	1	3.3%	0	0.0%
Nausea	[redacted]	[redacted]	1	3.3%	0	0.0%
Diarrhoea	[redacted]	[redacted]	1	3.3%	0	0.0%
Gastro-oesophageal reflux/other GI disorders	[redacted]	[redacted]	1	3.3%	0	0.0%
Asthenia/Somnolence	[redacted]	[redacted]	1	3.3%	0	0.0%
Dizziness	[redacted]	[redacted]	1	3.3%	0	0.0%
Blurred vision	[redacted]	[redacted]	4	13.3%	0	0.0%
Urinary difficulty/other renal or urinary disorder	[redacted]	[redacted]	1	3.3%	0	0.0%
Injection site pain	[redacted]	[redacted]	NA	NA	9	8.7%
Injection site bleeding	[redacted]	[redacted]	NA	NA	6	5.8%

Non-axillary sweating/hyperhidrosis	[redacted]	[redacted]	0	0.0%	6	5.8%

Abbreviations: AE, adverse event; CSR, clinical study report; GI, gastrointestinal; GPB, glycopyrronium bromide; N, number; U, units.
Source: Table 5.1.5, CSR[29]

Table 33: Two-week probability of AEs

	GPB 1% cream	Antimuscarinics	Botulinum toxin 100U
Dry eye	[redacted]	0.0%	0.0%
Dry mouth	[redacted]	14.4%	0.0%
Application site erythema/flush	[redacted]	1.1%	0.0%
Application site pruritus	[redacted]	0.0%	0.0%
Headache	[redacted]	1.1%	0.0%
Nausea	[redacted]	1.1%	0.0%
Diarrhoea	[redacted]	1.1%	0.0%
Gastro-oesophageal reflux/other GI disorders	[redacted]	1.1%	0.0%
Asthenia/Somnolence	[redacted]	1.1%	0.0%
Dizziness	[redacted]	1.1%	0.0%
Blurred vision	[redacted]	4.4%	0.0%
Urinary difficulty/other renal or urinary disorder	[redacted]	1.1%	0.0%
Injection site pain	[redacted]	NA	0.3%
Injection site bleeding	[redacted]	NA	0.2%
Non-axillary sweating/hyperhidrosis	[redacted]	0.0%	0.2%
Total	[redacted]	27.8%	0.8%

Abbreviations: AE, adverse event: GI, gastrointestinal; GPB, glycopyrronium bromide; U, unit.

3.4 Measurement and valuation of health effects

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

Patients health-related quality of life (HRQoL) was measured in the Phase 3a and 3b clinical trials for GPB 1% cream through the Hyperhidrosis Quality of Life (HidroQoL) and DLQI questionnaires.[29] In the comparative Phase 3a, the patient-rated outcome tools, HidroQoL, and DLQI, showed an improvement in both treatment groups, which was larger in the 1% GPB group than in the placebo group (Section 2).

3.4.2 Mapping

There is currently no validated mapping algorithm available to convert HidroQoL scores to EQ-5D.[58]

Although algorithms exist for mapping DLQI to EQ-5D, these have not been applied. The available algorithms were developed using data from broader dermatology populations (such as patients with psoriasis, atopic dermatitis, and other skin conditions) and may not adequately capture the specific burden and symptom profile experienced by individuals with PAHH. Furthermore, only aggregate data are available from the Phase 3a and 3b clinical trials, limiting the ability to account for patient-level heterogeneity or adjust for relevant covariates. As a result, applying mapping algorithms could produce overly simplistic and potentially biased utility estimates.

3.4.3 Health-related quality-of-life studies

An SLR has been conducted, with searches run 25 March 2025, to identify utility data in adult patients with HH from the published literature, including HTA documents. A detailed description of the search methodology, a PRISMA flow diagram, and results are presented in Appendix F.

Two studies were identified in the systematic literature review: Lee et al. (2021) and Kamudoni et al. (2014).[44,59]

Lee et al. (2021) reported EQ-5D-3L utility values for individuals with HH in South Korea, estimating values of 0.92 and 0.97 compared to the general population. However, the study provided no detail on disease characteristics or severity, and the authors noted that the results may not be generalisable beyond an Asian population.

Kamudoni et al. (2014), reported in abstract form, presented EQ-5D data from a 2013 longitudinal study of patients with HH recruited via online social networking communities. Mean utility scores decreased with increasing severity based on HDSS responses: 0.85 ± 0.13 (HDSS = 2), 0.80 ± 0.15 (HDSS = 3), and 0.69 ± 0.20 (HDSS = 4), with a statistically significant trend ($\chi^2 = 25.86$, df = 2, $p < 0.001$). Sample sizes were not reported.

3.4.4 Adverse reactions

Section 2.6.2.3 outlines the per-cycle probabilities of AEs. Their impact on HRQoL is captured using utility decrements sourced from the literature (Table 34). Where available, these values have been source from previous NICE appraisals in skin conditions (e.g., TA935 for hidradenitis suppurativa and TA986 for atopic dermatitis).[60,61] To minimise variability, utility decrements have, where possible, been taken from a single source (Sullivan et al. (2011)).[62] The utility decrement associated with non-axillary HH is based on the average disutilities from HDSS health states 2-4 relative to HDSS 1.

The duration of AEs is generally not well reported in the literature, except for injection site reactions related to botulinum toxin, for which Lowe et al. (2007) provides data. In the absence of further evidence, all other AEs are assumed to last for one model cycle (i.e., 14 days).[27]

Table 34: AE utility decrements and durations from the literature

	Utility decrement	Source[60–63]	Duration (days)	Source[27]
Dry eye	-0.00916	*Other eye disorders, Sullivan et al. (2011)*	14.00	*Assumption*
Dry mouth	-0.00235	*Assumed other inflammatory condition of the skin, Sullivan et al. (2011)*	14.00	*Assumption*
Application site erythema/flush	-0.00058	*Other skin disorders, Sullivan et al. (2011), NICE TA986*	14.00	*Assumption*
Application site pruritus	-0.00058	*Other skin disorders, Sullivan et al. (2011), NICE TA986*	14.00	*Assumption*
Headache	-0.02657	*Headache, Sullivan et al. (2011), NICE TA935*	14.00	*Assumption*
Nausea	-0.05120	*Other gastrointestinal disorders, Sullivan et al. (2011)*	14.00	*Assumption*
Diarrhoea	-0.05120	*Other gastrointestinal disorders, Sullivan et al. (2011), NICE TA935*	14.00	*Assumption*

Gastro-oesophageal reflux/other GI disorders	-0.07255	*Non-infectious gastroenteritis, Sullivan et al. (2011), NICE TA935*	14.00	*Assumption*
Asthenia/Somnolence	-0.02000	*Assumed deficiency and other anaemia, Sullivan et al. (2011)*	14.00	*Assumption*
Dizziness	-0.02657	*Assumed headache, Sullivan et al. (2011), NICE TA935*	14.00	*Assumption*
Blurred vision	0.00000	*Blindness and vision defects, Sullivan et al. (2011)*	14.00	*Assumption*
Urinary difficulty/other renal or urinary disorder	-0.07035	*Other diseases of bladder and urethra, Sullivan et al. (2011)*	14.00	*Assumption*
Injection site pain	-0.00400	*Zimmerman et al. (2018), NICE TA986*	2.40	*Lowe et al. (2007)*
Injection site bleeding	-0.00400	*Zimmerman et al. (2018), NICE TA986*	2.40	*Lowe et al. (2007)*
Non-axillary sweating/hyperhidrosis	-0.12182	*Assumption*	14.00	*Assumption*

Abbreviations: AE, adverse event.

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

Table 35 summarises the utility values used in the base case. Health state utilities for HDSS levels 2 to 4 are based on Kamudoni et al. (2014), while the utility for HDSS = 1 reflects the age-adjusted UK general population value from Alava-Hernandez et al. (2022), consistent with approaches used in the wider literature.[44,64]

Utility decrements for AEs, sourced from published studies, are applied per cycle by multiplying the decrement by both the duration and probability of the event occurring.

To reflect age-related decline in HRQoL over the model's lifetime horizon, age-adjustment multipliers from Alava-Hernandez et al. (2022) are applied to all utility values, in line with the NICE reference case.[46]

Table 35: Summary of utility values for cost-effectiveness analysis

State	Utility value	95% confidence interval	Reference in submission (section and page number)	Justification
Health state utility values				
HDSS=1	0.90	0.84 – 0.95	Section 3.8.2, Page 131	This assumption aligns with age- and gender-matched general population norms, consistent with published economic models in HH.[18,39,64]
HDSS=2	0.85	0.88 – 0.93	Section 3.4.3, Page 92	Aligning with EQ-5D values for HH published in the literature[44]
HDSS=3	0.80	0.84 – 0.90	Section 3.4.3, Page 92	
HDSS=4	0.69	0.76 – 0.84	Section 3.4.3, Page 92	
AE utility decrements				
Dry eye	-0.00916	-0.01095, -0.00736	Section 3.4.4, Page 93	Sourced from the literature[60–63]
Dry mouth	-0.00235	-0.00281, -0.00189	Section 3.4.4, Page 93	
Application site erythema/flush	-0.00058	-0.00069, -0.00047	Section 3.4.4, Page 93	
Application site pruritus	-0.00058	-0.00069, -0.00047	Section 3.4.4, Page 93	
Headache	-0.02657	-0.03178, -0.02136	Section 3.4.4, Page 93	
Nausea	-0.05120	-0.06124, -0.04117	Section 3.4.4, Page 93	
Diarrhoea	-0.05120	-0.06124, -0.04117	Section 3.4.4, Page 93	

Gastro-oesophageal reflux/other GI disorders	-0.07255	-0.08676, -0.05833	Section 3.4.4, Page 93	
Asthenia/Somnolence	-0.02000	-0.02392, -0.01608	Section 3.4.4, Page 94	
Dizziness	-0.02657	-0.03178, -0.02136	Section 3.4.4, Page 94	
Blurred vision	0.00000	0, 0	Section 3.4.4, Page 94	
Urinary difficulty/other renal or urinary disorder	-0.07035	-0.08414, -0.05656	Section 3.4.4, Page 94	
Injection site pain	-0.00400	-0.00478, -0.00322	Section 3.4.4, Page 94	
Injection site bleeding	-0.00400	-0.00478, -0.00322	Section 3.4.4, Page 94	
Non-axillary sweating/hyperhidrosis	-0.12182	-0.14569, -0.09794	Section 3.4.4, Page 94	Assumed based on the average disutilities from HDSS health states 2-4 relative to HDSS 1

Abbreviations: AE, adverse event; HDSS, Hyperhidrosis Disease Severity Score.

3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR has been conducted, with searches run 25 March 2025, to identify cost and resource use data in the management of adult patients with HH from the published literature, including HTA documents. A detailed description of the search methodology, a PRISMA flow diagram, and results are presented in Appendix G.

Six studies were identified in the SLR. Studies considered a Brazilian, US, UK, Irish, Spanish, and an Italian perspective. The UK study (Wade et al. (2017)) was also identified in the economic model SLR (Appendix G) and has informed the structure and assumptions underpinning this appraisal – as referenced throughout the document. Cost and resource use items which are relevant to this submission are summarised below.

- **Medications in UK clinical practice:** Wade et al. (2017) assumed medications for PAHH include propantheline bromide (75 mg/day), oxybutynin (12.5 mg/day), and oral GPB (2 mg/day). In the base case, Wade et al. (2017) assumed 100% use of propantheline bromide. This appraisal adopts the following daily doses: 75 mg for propantheline bromide, 7.5 mg for oxybutynin, and 2 mg for oral GPB. The dose for oxybutynin differs from Wade et al. (2017), as it aligns with Schollhammer et al. (2015) which informs the ITCs in this appraisal. A scenario analysis considers the impact of 12.5mg a day for oxybutynin. This appraisal assumes: 35.4% propantheline bromide, 46.2% oxybutynin, and 18.5% oral GPB, reflecting feedback from the UK-based survey reported in Wade et al. (2017).
- **Botulinum toxin costs:** In Wade et al. (2017), the cost of botulinum toxin was based on the equivalent NHS reference cost (Healthcare Resource Group code JC42A, Intermediate Skin Procedures, 13 years and over, General Surgery category). To support inclusion of this NHS reference cost, an additional cost for a botulinum toxin procedure was estimated based on the BNF cost of 100U of botulinum toxin and the cost of a nurse grade 5 delivering the procedure, as advised by clinical experts. This appraisal adopts the same approach, sourcing the costs from the most recent NHS Reference Costs 2023/24, BNF, and PSSRU 2024. Additionally, the base case dose of botulinum toxin aligns with Wade et al. (2017).
- **Botulinum toxin re-treatment schedule:** Wade et al. (2017) assumed botulinum toxin injections were given every 6 months, based on clinical evidence suggesting that the effectiveness of botulinum toxin may be sustained over a 6 month period. This appraisal assumes the same re-treatment rate in the base case.
- **Iontophoresis and surgery:** Wade et al. (2017) included iontophoresis and surgery. As described in Section 2, these are not included in this appraisal due to their extremely limited use in UK clinical practice, as reflected in the comparator list in the NICE final scope and by feedback from clinical experts in the scoping workshop for this appraisal.[50]
- **Monitoring:** Wade et al. (2017) assumed follow-up visits every 3 months. This appraisal assumes this frequency for the first year, reducing to 12 months for subsequent years – aligning with UK clinical feedback[12]

Costs reflect the latest available source i.e. BNF accessed May 2025, NHS Reference Costs 2023/24, and the PSSRU 2024.[47–49]

3.5.1 Intervention and comparators' costs and resource use

3.5.1.1 Acquisition costs

The anticipated acquisition costs for GPB 1% cream are shown in Table 36, with unit costs sourced from data on file (Leith Healthcare).[12] The cost per administration is £[redacted], calculated using unit price, dosing, and compliance assumptions (Section 3.2.3.13.5.1). Treatment duration is detailed in Section 3.3.3.

Table 36: GPB 1% cream | Anticipated acquisition costs

	Cost/pack (£)	Units	Pack size	Dose/administration
GPB 1% cream	[redacted]	50g	1	1.08

Abbreviations: GPB, glycopyrronium bromide

Acquisition costs for antimuscarinics are based on propantheline bromide, oxybutynin, and oral GPB. Table 37 presents the unit costs, sourced from the BNF and NHS Drug Tariff.[23,47]

For propantheline bromide, prices on the BNF range from £20.74 to £195.14. Due to recent supply shortages of the lower-cost formulation, higher-cost packs are now more commonly used in UK clinical practice. This shift is reflected in national prescribing data, which show a marked increase in total spending from January 2024.[65] Accordingly, the higher cost of £103.52 is used in the base case to reflect current UK clinical practice, with a scenario analysis assessing the impact of the lower £20.74 cost.[66]

The daily cost is calculated by multiplying the unit cost per administration by the number of administrations per day and compliance (Section 3.2.3.2), and then weighted across the three antimuscarinics based on usage distribution (Table 25), resulting in a daily cost of £2.88. Treatment duration with antimuscarinics is discussed in Section 3.3.3.

Table 37: Oral antimuscarinics | Acquisition costs

Medication	Cost/pack (£)	Units	Pack size	Dose/ administration	Administrations / day	Source
Propantheline bromide	£103.52	15.0 mg	112	15	5	BNF, accessed May 2025[47]
Oxybutynin	£1.40	2.5 mg	84	2.5	3	BNF, accessed May 2025
Oral GPB	£198.00	2.0 mg	30	2	1	NHS Drug Tariff, accessed May 2025[23]

Abbreviations: BNF, British National Formulary; GPB, glycopyrronium bromide; mg, milligram; NHS, National Health Service.

Acquisition costs for botulinum toxin based on Botox® and Dysport®, with unit costs presented in Table 38 and sourced from the BNF. The economic model assumes a dose of 100U (50U per axilla), as outlined in Section 3.2.3.2. Since only Botox® is available in a 100U formulation, it is used in the base case, resulting in an acquisition cost of £129.90 per procedure. Treatment duration is detailed in Section 3.3.3.

Table 38: Botulinum toxin | Procedure costs

	Weight	Cost/pack (£)	Units	Pack size	Dose/ procedure	Cost/ procedure	Source
Botox	0.0%	£65.00	50 U	1	100	£130.00	BNF, accessed April 2025
Botox	100.0%	£129.90	100 U	1	100	£129.90	
Botox	0.0%	£134.82	125 U	2	100	£134.82	
Botox	0.0%	£259.80	200 U	1	100	£259.80	
Dysport	0.0%	£92.40	300 U	1	200	£92.40	

Dysport	0.0%	£308.00	500 U	2	200	£308.00

Abbreviations: BNF, British National Formulary; U,unit.

3.5.1.2 Administration and monitoring costs

Table 39 presents the costs associated with administering therapy and monitoring for patients with severe PAHH in both primary and secondary care settings, sourced from PSSRU 2024 and NHS Reference Costs 2023/24, respectively.[48,49]

According to feedback from a UK clinical expert, and as reflected in recent NHS initiatives, general practitioners (GPs) in England are now encouraged to use advice and guidance (A&G) services with hospital specialists to help reduce elective care referrals. In line with UK clinical expert feedback, this approach is relevant for the management of severe PAHH, with GPs being advised to treat these patients within primary care where appropriate, rather than referring to secondary care. Therefore, an A&G interaction, costed at £20, is added to the cost of a standard GP appointment to reflect the total cost of administration and monitoring in the primary care setting where A&G is required. This may underestimate the true cost, as in practice, two GP appointments may be required - one before and one after the A&G interaction. However, A&G is considered more relevant to the use of antimuscarinics, which are more challenging to manage due to their side effect profile - making this a conservative assumption. A&G is particularly relevant to antimuscarinics because propantheline bromide is the only antimuscarinic licensed for HH, and GPs are generally reluctant to prescribe unlicensed treatments without input from secondary care. Feedback from three UK dermatologists supports this, noting that GPs in their regions typically avoid prescribing antimuscarinics due to the complexities involved in their management.[12]

The additional administration costs specific to botulinum toxin procedures are based on the 2023/24 NHS Reference Costs for intermediate skin procedures, combined with the cost of 45 minutes of a Band 5 nurse. These assumptions are consistent with those used in Wade et al. (2017).[48,49]

Table 39: Administration and monitoring costs relevant to severe PAHH

	Cost (£)	Source[48,49]
Costs relevant to all therapies		
Primary care appointment	£45.00	*PSSRU 2024; Unit costs for a GP per surgery consultation lasting 10 minutes*
Primary care appointment and A&G	£65.00	*Primary care consultation plus £20 for A&G*
Secondary care appointment	£168.00	*NHS Reference Costs 2023/2024; Outpatient care, Dermatology Service, WF01A, Non-admitted face-to-face attendance, consultant-led, follow-up*
Costs relevant to botulinum toxin		

Botulinum toxin procedure	£156.00	NHS Reference Costs 2023/24, HRG code JC42A, Intermediate Skin Procedures, 19 years and over, General Surgery category
Cost of delivery of botulinum toxin procedure	£35.25	Table 9.2.1, PSSRU 2024, 45 minutes × hourly rate of nurse grade 5

Abbreviations: A&G, advice and guidance; GPB, glycopyrronium bromide; HRG, Healthcare Resource Group; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Table 40 outlines the administration and monitoring resource use assumptions for GPB 1% cream, antimuscarinics, and botulinum toxin.

For GPB 1% cream, it is assumed that 100% of administration and monitoring occurs in primary care, without the need for A&G. Patients are assumed to have quarterly appointments during the first year of treatment, followed by annual appointments thereafter.

For antimuscarinics, it is assumed that 25% of patients are initiated in primary care, 25% in primary care following A&G, and 50% in secondary care. Monitoring follows the same schedule as GPB 1% cream: quarterly in year one, then annually.

Botulinum toxin must be administered by a specialist in a secondary care setting; therefore, 100% of administration and monitoring occurs in secondary care. Monitoring follows the same schedule as GPB 1% cream and antimuscarinics: quarterly during the first year, then annually thereafter. These costs are applied in addition to the procedural costs (which are only applied upon administration of botulinum toxin) shown in Table 39.

Table 40: Administration and monitoring schedule

	GPB 1% cream	Antimuscarinics	Botulinum toxin
Primary care	100%	25%	0%
Primary care and A&G	0%	25%	0%
Secondary care	0%	50%	100%
Monitoring year 1	Every 3-months	Every 3-months	Every 3-months
Monitoring year 2+	Every 12-months	Every 12-months	Every 12-months

Abbreviations: A&G, advice and guidance; GPB, glycopyrronium bromide.

3.5.2 Health-state unit costs and resource use

Costs accrued within the HDSS health states include only acquisition, administration, and monitoring costs, as detailed above.

Upon transition to the subsequent therapy health state, the model applies a weighted cost based on the distribution of subsequent therapies. These subsequent therapies include antimuscarinics (administered in primary care, primary care with A&G, or secondary care), botulinum toxin (secondary care only), and unlicensed GPB (secondary care only).

The costs of subsequent therapies are calculated by summing the acquisition, administration and monitoring, and AE costs incurred during initial treatment. For instance, the one-off cost of subsequent antimuscarinics in the primary care setting is based on the total of these cost components from initial antimuscarinic therapy, assuming 100% of administration and monitoring occurs in primary care.

For subsequent use of unlicensed GPB, which is only available in secondary care in the UK, the one-off cost is derived using a cost multiplier. This multiplier reflects the cost per administration of unlicensed GPB relative to GPB 1% cream. It is then applied to the acquisition cost of initial GPB 1% cream, and combined with the administration, monitoring, and AE costs associated with initial GPB 1% cream - assuming 100% administration in secondary care.

Table 41 presents the one-off costs of subsequent therapies. Table 42 details the unit cost of unlicensed GPB based on the NHS Drug Tariff and the calculated multiplier applied to GPB 1% cream. The same dosage is assumed for both unlicensed GPB and GPB 1% cream.

Table 41: One-off costs associated with subsequent therapies

	Cost (£)	Source
Antimuscarinics (primary care)	£1,089	Assumed same cost as acquisition, administration, monitoring, and AE costs from initial antimuscarinics and 100% primary care
Antimuscarinics (primary care and A&G)	£1,135	Assumed same cost as acquisition, administration, monitoring, and AE costs from initial antimuscarinics and 100% primary care and A&G
Antimuscarinics (secondary care)	£1,370	Assumed same cost as acquisition, administration, monitoring, and AE costs from initial antimuscarinics and 100% secondary care
Botulinum toxin (secondary care)	£1,704	Assumed same cost as acquisition, administration, monitoring, and AE costs from initial botulinum toxin and 100% secondary care
Unlicensed GPB (secondary care)	£3,911	Assumed multiplier for acquisition costs for GPB 1% cream vs. unlicensed GPB, administration, monitoring and AE costs from initial GPB 1% cream and 100% secondary care

Abbreviations: A&G, advice and guidance; AE, adverse event; GPB, glycopyrronium bromide.

Table 42: Unit costs of unlicensed GPB

	Unlicensed GPB
Cost/pack (£)	£129.70

Units	30g
Pack size	1
Dose/ administration	1.08
Compliance	[redacted]
Cost/ administration	£3.53
Multiplier relative to GPB 1% cream	3.1

Abbreviations: GPB, glycopyrronium bromide.

Table 43 presents the assumed distribution of subsequent therapies following each initial treatment option.

For patients who discontinue GPB 1% cream and require further treatment, it is assumed they are referred to secondary care. Of these, 10% receive antimuscarinics and 90% receive botulinum toxin. This results in a one-off cost of £1,670.

For patients discontinuing antimuscarinics, it is assumed that 10% receive a different antimuscarinic, 85% receive botulinum toxin, and 5% receive unlicensed GPB in secondary care. This results in a one-off cost of £1,781.

For those who discontinue botulinum toxin, it is assumed that 50% transition to antimuscarinics and 50% to unlicensed GPB. This results in a one-off cost of £2,640.

Table 43: Distribution of subsequent therapies

	Proportion of subsequent therapies after initial:		
	GPB 1% cream	Antimuscarinics	Botulinum toxin
Antimuscarinics (primary care)	0.0%	0.0%	0.0%
Antimuscarinics (primary care and A&G)	0.0%	0.0%	0.0%
Antimuscarinics (secondary care)	10.0%	10.0%	50.0%
Botulinum toxin (secondary care)	90.0%	85.0%	0.0%
Unlicensed GPB (secondary care)	0.0%	5.0%	50.0%

Abbreviations: A&G, advice and guidance; GPB, glycopyrronium bromide.

3.5.3 Adverse reaction unit costs and resource use

Section 2.6.2.3 outlines the per-cycle probabilities of AEs, with associated costs presented in Table 44. These costs are multiplied by the per-cycle probabilities to calculate the weighted average AE cost per cycle: £0.45 for GPB 1% cream, £15.14 for antimuscarinics, and £3.44 for botulinum toxin.

Table 44: AE costs

	Cost (£)	Source[48]
Dry eye	£54.50	PSSRU 2024; Unit costs for a GP per surgery consultation lasting 10 minutes plus 10 minutes of a community-based pharmacist (band 6)
Dry mouth	£54.50	PSSRU 2024; Unit costs for a GP per surgery consultation lasting 10 minutes plus 10 minutes of a community-based pharmacist (band 6)
Application site erythema/flush	£54.50	PSSRU 2024; Unit costs for a GP per surgery consultation lasting 10 minutes plus 10 minutes of a community-based pharmacist (band 6)
Application site pruritus	£54.50	PSSRU 2024; Unit costs for a GP per surgery consultation lasting 10 minutes plus 10 minutes of a community-based pharmacist (band 6)
Headache	£54.50	PSSRU 2024; Unit costs for a GP per surgery consultation lasting 10 minutes plus 10 minutes of a community-based pharmacist (band 6)
Nausea	£54.50	PSSRU 2024; Unit costs for a GP per surgery consultation lasting 10 minutes plus 10 minutes of a community-based pharmacist (band 6)
Diarrhoea	£54.50	PSSRU 2024; Unit costs for a GP per surgery consultation lasting 10 minutes plus 10 minutes of a community-based pharmacist (band 6)
Gastro-oesophageal reflux/other GI disorders	£54.50	PSSRU 2024; Unit costs for a GP per surgery consultation lasting 10 minutes plus 10 minutes of a community-based pharmacist (band 6)
Asthenia/Somnolence	£54.50	PSSRU 2024; Unit costs for a GP per surgery consultation lasting 10 minutes plus 10 minutes of a community-based pharmacist (band 6)
Dizziness	£54.50	PSSRU 2024; Unit costs for a GP per surgery consultation lasting 10 minutes plus 10 minutes of a community-based pharmacist (band 6)
Blurred vision	£54.50	PSSRU 2024; Unit costs for a GP per surgery consultation lasting 10 minutes plus 10 minutes of a community-based pharmacist (band 6)
Urinary difficulty/other renal or urinary disorder	£54.50	PSSRU 2024; Unit costs for a GP per surgery consultation lasting 10 minutes plus 10 minutes of a community-based pharmacist (band 6)

Injection site pain	£9.17	PSSRU 2024; Unit costs for 10 minutes of a hospital-based pharmacist (band 6)
Injection site bleeding	£9.17	PSSRU 2024; Unit costs for 10 minutes of a hospital-based pharmacist (band 6)
Non-axillary sweating/hyperhidrosis	£1,624.64	Assumed the same cost as antimuscarinics in secondary care (acquisition plus administration)

Abbreviations: AE, adverse event; GI, gastrointestinal; GP, general practitioner; PSSRU, Personal Social Services Research Unit.

3.6 Severity

GPB 1% cream does not meet the criteria for the severity modifier in adults with severe PAHH (Table 45).

Absolute and proportional QALY shortfalls have been calculated in line with the NICE methods guide.[46] QALYs for the general population without PAHH were estimated using UK life tables from the Office for National Statistics (2021–2023), consistent with the background mortality assumptions in the economic model, and utilities from Hernandez-Alava et al. (2022).[64,67]

A mean starting age of 35.6 years and a 52.9% female population were assumed, based on the FASb population (Table 21). Life years and QALYs were discounted at 3.5%.

In the absence of disease, individuals are expected to accrue 19.7 discounted QALYs. For patients with severe PAHH, the model estimates a maximum of 17.3 discounted QALYs with antimuscarinics or botulinum toxin, resulting in an absolute shortfall of 2.4 QALYs and a proportional shortfall of 0.12.

Table 45: Summary of QALY shortfall analysis

Expected total discounted QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute and proportional QALY shortfall
19.7	17.3	2.4, 0.12

Abbreviations: QALY, quality-adjusted life year.

3.7 Uncertainty

The nature of severe PAHH poses several challenges to generating high-quality clinical evidence:

- **Subjectivity of symptoms and outcomes:** PAHH has a significant impact on quality of life but does not affect mortality, limiting the use of objective clinical endpoints such as survival. As a result, clinical studies rely heavily on patient-reported outcomes, including the HDSS, HidroQoL, and DLQI. These tools are inherently subjective and dependent on self-reporting, which introduces variability, limits blinding, and complicates the standardisation of outcomes across studies.
- **Short-term, episodic, and individualised treatment patterns:** Most treatments for PAHH are used on a short-term or episodic basis. This makes it difficult to conduct long-term RCTs, as demonstrated by high dropout rates in botulinum toxin studies and the short durations of trials evaluating oxybutynin. The Phase 3b trial for GPB 1% cream also showed variable compliance and frequency of application over time. Furthermore, treatment is often tailored to the individual, and patients may engage in varying degrees of self-management, making it challenging to attribute outcomes directly to specific interventions.
- **Barriers to trial participation:** Although PAHH is relatively common, it is often underdiagnosed. Stigma and embarrassment can deter individuals from seeking treatment or participating in clinical studies, further limiting the available evidence base and making recruitment for trials more difficult.
- **Healthcare system variability and access issues:** Management of PAHH varies widely by geography, clinical setting (primary vs secondary care), and clinician expertise. For example, access to botulinum toxin treatment differs across NHS Trusts in the UK. In some cases, patients turn to private healthcare or self-fund treatment due to long NHS waiting lists or easier access to services through private providers (e.g. botulinum toxin offered via high street clinics). This heterogeneity affects both treatment pathways and the generalisability of trial findings.
- **Limited investment in research:** As a non-life-threatening condition with several off-label or relatively low-cost treatments, PAHH has historically attracted limited research funding. Consequently, the evidence base is dominated by small-scale, industry-

sponsored trials. This was reflected in the limited number of robust studies identified in the clinical systematic literature review.

Despite the challenges associated with generating high-quality evidence in severe PAHH, GPB 1% cream has been robustly evaluated in both short- and long-term settings. It has been assessed in a randomised, placebo-controlled trial (Phase 3a) with a 29-day follow-up and further supported by long-term data from the Phase 3b extension study, which followed patients for up to 72 weeks – this is one of the longest follow-ups in PAHH. Having data over this extended period is particularly valuable in a condition where long-term outcomes are difficult to capture.

While the modelled treatment effect is based on the subjective HDSS score, the clinical trials for GPB 1% cream also collected objective gravimetric sweat production data, which aligned with the HDSS findings and further supports the efficacy of GPB 1% cream.

In the base case, the ITCs use the FASa, which includes patients who did not fully adhere to the treatment protocol. While the treatment effect in this group is smaller than in the PPSa population, it is more reflective of real-world use, where patients often self-manage and tailor treatment to their needs. This provides a more realistic estimate of effectiveness in clinical practice, where flexibility and adherence vary.

Importantly, GPB 1% cream offers a practical solution to some of the structural barriers in the current healthcare pathway. It can be prescribed in the primary care setting, avoiding the need for referral to secondary care or A&G from dermatologists. Its favourable and manageable side effect profile means GPs should feel confident prescribing it after first-line failure with aluminium-based antiperspirants. This represents a meaningful cost and time saving for the NHS and directly supports national initiatives aimed at reducing elective care backlogs.

3.8 Summary of base-case analysis inputs and assumptions

3.8.1 Summary of base-case analysis inputs

Table 46 presents the base case inputs, as well as the measurement of uncertainty and distribution, and the reference to the relevant Section in this submission.

Table 46: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Settings			
Time horizon	65	NA	

Discount rate - costs	3.5%	NA	Section 3.2.2, Page 73
Discount rate - outcomes	3.5%	NA	
Baseline characteristics			
Proportion female	52.9%	48.6% - 57.2% (Beta)	Section 3.2.1, Page 71
Age at baseline	35.6	34.6 - 36.6 (Normal)	
Proportion HDSS 1 at baseline	[redacted]	[redacted]	
Proportion HDSS 2 at baseline	[redacted]	[redacted]	
Proportion HDSS 3 at baseline	[redacted]	[redacted]	
Proportion HDSS 4 at baseline	[redacted]	[redacted]	
GPB 1% cream transitions			
GPB 1% cream (FASb): proportion ≥2, week 4	[redacted]	[redacted]	Section 3.3.1, page 80
GPB 1% cream (FASb): proportion ≥2, week 8	[redacted]	[redacted]	
GPB 1% cream (FASb): proportion ≥2, week 12	[redacted]	[redacted]	
GPB 1% cream (FASb): proportion ≥2, week 28	[redacted]	[redacted]	
GPB 1% cream (FASb): proportion ≥2, week 52	[redacted]	[redacted]	
GPB 1% cream (FASb): proportion ≥2, week 72	[redacted]	[redacted]	
GPB 1% cream (FASb): proportion ≥1, week 4	[redacted]	[redacted]	
GPB 1% cream (FASb): proportion ≥1, week 8	[redacted]	[redacted]	
GPB 1% cream (FASb): proportion ≥1, week 12	[redacted]	[redacted]	
GPB 1% cream (FASb): proportion ≥1, week 28	[redacted]	[redacted]	

GPB 1% cream (FASb): proportion ≥1, week 52	[redacted]	[redacted]	
GPB 1% cream (FASb): proportion ≥1, week 72	[redacted]	[redacted]	
GPB 1% cream (FASb): proportion 1 or 2, week 4	[redacted]	[redacted]	
GPB 1% cream (FASb): proportion 1 or 2, week 8	[redacted]	[redacted]	
GPB 1% cream (FASb): proportion 1 or 2, week 12	[redacted]	[redacted]	
GPB 1% cream (FASb): proportion 1 or 2, week 28	[redacted]	[redacted]	
GPB 1% cream (FASb): proportion 1 or 2, week 52	[redacted]	[redacted]	
GPB 1% cream (FASb): proportion 1 or 2, week 72	[redacted]	[redacted]	
Comparative efficacy			
Odds ratio: GPB 1% cream vs. antimuscarinics ≥2 HDSS response	[redacted]	[redacted]	Section 3.3.2, Page 83
Odds ratio: GPB 1% cream vs. antimuscarinics ≥1 HDSS response	[redacted]	[redacted]	
Odds ratio: GPB 1% cream vs. botulinum toxin (1st treatment) ≥2 HDSS response	[redacted]	[redacted]	
Odds ratio: GPB 1% cream vs. botulinum toxin (2nd+ treatment) ≥2 HDSS response	[redacted]	[redacted]	
Proportion of AEs			
GPB 1% cream: 2-week proportion of AEs, Dry eye	[redacted]	[redacted]	Section 3.3.5, Page 91
GPB 1% cream: 2-week proportion of AEs, Dry mouth	[redacted]	[redacted]	

GPB 1% cream: 2-week proportion of AEs, Application site erythema/flush	[redacted]	[redacted]
GPB 1% cream: 2-week proportion of AEs, Application site pruritus	[redacted]	[redacted]
GPB 1% cream: 2-week proportion of AEs, Headache	[redacted]	[redacted]
GPB 1% cream: 2-week proportion of AEs, Nausea	[redacted]	[redacted]
GPB 1% cream: 2-week proportion of AEs, Diarrhoea	[redacted]	[redacted]
GPB 1% cream: 2-week proportion of AEs, Gastro-oesophageal reflux/gastrointestinal discomfort/abdominal pain upper	[redacted]	[redacted]
GPB 1% cream: 2-week proportion of AEs, Asthenia/Somnolence	[redacted]	[redacted]
GPB 1% cream: 2-week proportion of AEs, Dizziness	[redacted]	[redacted]
GPB 1% cream: 2-week proportion of AEs, Blurred vision	[redacted]	[redacted]
GPB 1% cream: 2-week proportion of AEs, Urinary difficulty/frequent urination/urinary retention/bladder discomfort	[redacted]	[redacted]
GPB 1% cream: 2-week proportion of AEs, Injection site pain	[redacted]	[redacted]
GPB 1% cream: 2-week proportion of AEs, Injection site bleeding	[redacted]	[redacted]

GPB 1% cream: 2-week proportion of AEs, Non-axillary sweating/hyperhidrosis	[redacted]	[redacted]
Antimuscarinics: 2-week proportion of AEs, Dry eye	0.0%	0% - 4% (Beta)
Antimuscarinics: 2-week proportion of AEs, Dry mouth	14.4%	8.7% - 23.2% (Beta)
Antimuscarinics: 2-week proportion of AEs, Application site erythema/flush	1.1%	0.3% - 6% (Beta)
Antimuscarinics: 2-week proportion of AEs, Application site pruritus	0.0%	0% - 4% (Beta)
Antimuscarinics: 2-week proportion of AEs, Headache	1.1%	0.3% - 6% (Beta)
Antimuscarinics: 2-week proportion of AEs, Nausea	1.1%	0.3% - 6% (Beta)
Antimuscarinics: 2-week proportion of AEs, Diarrhoea	1.1%	0.3% - 6% (Beta)
Antimuscarinics: 2-week proportion of AEs, Gastro-oesophageal reflux/gastrointestinal discomfort/abdominal pain upper	1.1%	0.3% - 6% (Beta)
Antimuscarinics: 2-week proportion of AEs, Asthenia/Somnolence	1.1%	0.3% - 6% (Beta)
Antimuscarinics: 2-week proportion of AEs, Dizziness	1.1%	0.3% - 6% (Beta)
Antimuscarinics: 2-week proportion of AEs, Blurred vision	4.4%	1.8% - 10.9% (Beta)
Antimuscarinics: 2-week proportion of AEs, Urinary difficulty/frequent	1.1%	0.3% - 6% (Beta)

urination/urinary retention/bladder discomfort		
Antimuscarinics: 2-week proportion of AEs, Injection site pain	0.0%	0% - 4% (Beta)
Antimuscarinics: 2-week proportion of AEs, Injection site bleeding	0.0%	0% - 4% (Beta)
Antimuscarinics: 2-week proportion of AEs, Non-axillary sweating/hyperhidrosis	0.0%	0% - 4% (Beta)
Botulinum toxin 100-U: 2-week proportion of AEs, Dry eye	0.0%	0% - 0.1% (Beta)
Botulinum toxin 100-U: 2-week proportion of AEs, Dry mouth	0.0%	0% - 0.1% (Beta)
Botulinum toxin 100-U: 2-week proportion of AEs, Application site erythema/flush	0.0%	0% - 0.1% (Beta)
Botulinum toxin 100-U: 2-week proportion of AEs, Application site pruritus	0.0%	0% - 0.1% (Beta)
Botulinum toxin 100-U: 2-week proportion of AEs, Headache	0.0%	0% - 0.1% (Beta)
Botulinum toxin 100-U: 2-week proportion of AEs, Nausea	0.0%	0% - 0.1% (Beta)
Botulinum toxin 100-U: 2-week proportion of AEs, Diarrhoea	0.0%	0% - 0.1% (Beta)
Botulinum toxin 100-U: 2-week proportion of AEs, Gastro-oesophageal reflux/gastrointestinal discomfort/abdominal pain upper	0.0%	0% - 0.1% (Beta)

Botulinum toxin 100-U: 2-week proportion of AEs, Asthenia/Somnolence	0.0%	0% - 0.1% (Beta)	
Botulinum toxin 100-U: 2-week proportion of AEs, Dizziness	0.0%	0% - 0.1% (Beta)	
Botulinum toxin 100-U: 2-week proportion of AEs, Blurred vision	0.0%	0% - 0.1% (Beta)	
Botulinum toxin 100-U: 2-week proportion of AEs, Urinary difficulty/frequent urination/urinary retention/bladder discomfort	0.0%	0% - 0.1% (Beta)	
Botulinum toxin 100-U: 2-week proportion of AEs, Injection site pain	0.3%	0.2% - 0.6% (Beta)	
Botulinum toxin 100-U: 2-week proportion of AEs, Injection site bleeding	0.2%	0.1% - 0.5% (Beta)	
Botulinum toxin 100-U: 2-week proportion of AEs, Non-axillary sweating/hyperhidrosis	0.2%	0.1% - 0.5% (Beta)	
Acquisitions, administration, and monitoring			
Number of botulinum toxin procedures per year	2.0	1.6 – 2.4 (Normal)	Section 3.8.2, Page 128
GPB 1% cream: cost per pack	[redacted]	NA	Section 3.5.1.1, Page 99
GPB 1% cream: difference between the amount of product use and the amount of product use according to protocol	[redacted]	[redacted]	Section 3.2.3.1, Page 76
GPB 1% cream: proportion primary care administration/monitoring	100.0%	99.7% - 100% (Beta tree)	Section 3.2.3.1, Page 102

GPB 1% cream: proportion primary care and A&G administration/monitoring	0.0%	0% - 0% (Beta tree)	
GPB 1% cream: proportion secondary care	0.0%	0.3% - 0% (Beta tree)	
Antimuscarinics: proportion primary care administration/monitoring	25.0%	22.4% - 27.7% (Beta tree)	
Antimuscarinics: proportion primary care and A&G administration/monitoring	25.0%	23.3% - 26.6% (Beta tree)	
Antimuscarinics: proportion secondary care	50.0%	54.3% - 45.7% (Beta tree)	
Botulinum toxin: proportion primary care administration/monitoring	0.0%	0% - 0.3% (Beta tree)	
Botulinum toxin: proportion primary care and A&G administration/monitoring	0.0%	0% - 0.3% (Beta tree)	
Botulinum toxin: proportion secondary care	100.0%	100% - 99.5% (Beta tree)	
Proportion antimuscarinics: propantheline bromide	35.4%	32.5% - 38.4% (Beta tree)	
Proportion antimuscarinics: oxybutynin	46.2%	45.9% - 46.1% (Beta tree)	
Proportion antimuscarinics: oral GPB	18.5%	21.7% - 15.5% (Beta tree)	
Propantheline bromide: cost per pack	£103.52	£83.23 - £123.81 (Normal)	Section 3.5.1.1, Page 99
Oxybutynin: cost per pack	£1.40	£1.13 - £1.67 (Normal)	
Glycopyrronium bromide: cost per pack	£198.00	£159.19 - £236.81 (Normal)	
Propantheline bromide: compliance	100.0%	96.4% - 100% (Beta)	
Oxybutynin: compliance	100.0%	96.4% - 100% (Beta)	

Glycopyrronium bromide: compliance	100.0%	96.4% - 100% (Beta)	
Proportion botulinum toxin: Botox 50U	0.00	0% - 0.3% (Beta tree)	Section 3.5.1.1, Page 100
Proportion botulinum toxin: Botox 100U	1.00	99.7% - 99.7% (Beta tree)	
Proportion botulinum toxin: Botox 125U	0.00	0% - 0% (Beta tree)	
Proportion botulinum toxin: Botox 200U	0.00	0% - 0% (Beta tree)	
Proportion botulinum toxin: Dysport 300U	0.00	0% - 0% (Beta tree)	
Proportion botulinum toxin: Dysport 500U	0.00	0.2% - 0% (Beta tree)	
Botox 50U: cost per pack	£65.00	£52.26 - £77.74 (Normal)	
Botox 100U: cost per pack	£129.90	£104.44 - £155.36 (Normal)	
Botox 125U: cost per pack	£134.82	£108.4 - £161.24 (Normal)	
Botox 200U: cost per pack	£259.80	£208.88 - £310.72 (Normal)	
Dysport 300U: cost per pack	£92.40	£74.29 - £110.51 (Normal)	
Dysport 500U: cost per pack	£308.00	£247.63 - £368.37 (Normal)	
Cost of primary care appointment	£45.00	£36.18 - £53.82 (Normal)	Section 3.5.1.2, Page 101
Cost of primary care and A&G appointment	£65.00	£52.26 - £77.74 (Normal)	
Cost of secondary care appointment	£168.00	£164.86 - £171.14 (Normal)	
Cost of Botulinum toxin procedure	£156.00	£125.42 - £186.58 (Normal)	

Cost of nurse time for Botulinum toxin procedure	£35.25	£28.34 - £42.16 (Normal)	
Unlicensed GPB: cost per tube	£129.70	£104.28 - £155.12 (Normal)	
Subsequent therapy costs			
Subsequent therapy costs: Antimuscarinics (primary care)	£1,089	£875.66 - £1302.59 (Normal)	Section 3.5.2, Page 103
Subsequent therapy costs: Antimuscarinics (primary care and A&G)	£1,135	£912.33 - £1357.14 (Normal)	
Subsequent therapy costs: Antimuscarinics (secondary care)	£1,370	£1101.18 - £1638.06 (Normal)	
Subsequent therapy costs: Botulinum toxin (secondary care)	£1,704	£1369.66 - £2037.44 (Normal)	
Subsequent therapy costs: Unlicensed GPB (secondary care)	£3,911	£3144.45 - £4677.53 (Normal)	
GPB 1% cream: proportion antimuscarinics (primary care) subsequent therapy	0.0%	0% - 0% (Beta)	
GPB 1% cream: proportion antimuscarinics (primary care and A&G) subsequent therapy	0.0%	0% - 0% (Beta)	
GPB 1% cream: proportion antimuscarinics (secondary care) subsequent therapy	10.0%	5% - 16.6% (Beta)	
GPB 1% cream: proportion Botulinum toxin (secondary care) subsequent therapy	90.0%	83.4% - 95% (Beta)	
GPB 1% cream: proportion unlicensed GPB (secondary care) subsequent therapy	0.0%	0% - 0% (Beta)	

Antimuscarinics: proportion antimuscarinics (primary care) subsequent therapy	0.0%	0% - 0% (Beta)	
Antimuscarinics: proportion antimuscarinics (primary care and A&G) subsequent therapy	0.0%	0% - 0% (Beta)	
Antimuscarinics: proportion antimuscarinics (secondary care) subsequent therapy	10.0%	5% - 16.6% (Beta)	
Antimuscarinics: proportion Botulinum toxin (secondary care) subsequent therapy	85.0%	77.4% - 91.3% (Beta)	
Antimuscarinics: proportion unlicensed GPB (secondary care) subsequent therapy	5.0%	1.7% - 10% (Beta)	
Botulinum toxin: proportion antimuscarinics (primary care) subsequent therapy	0.0%	0% - 0% (Beta)	
Botulinum toxin: proportion antimuscarinics (primary care and A&G) subsequent therapy	0.0%	0% - 0% (Beta)	
Botulinum toxin: proportion antimuscarinics (secondary care) subsequent therapy	50.0%	40.3% - 59.7% (Beta)	
Botulinum toxin: proportion Botulinum toxin (secondary care) subsequent therapy	0.0%	0% - 0% (Beta)	
Botulinum toxin: proportion unlicensed GPB (secondary care) subsequent therapy	50.0%	40.3% - 59.7% (Beta)	
AE costs			
AE costs: Dry eye	54.50	£43.82 - £65.18 (Normal)	Section 3.5.3, Page 105
AE costs: Dry mouth	54.50	£43.82 - £65.18 (Normal)	

AE costs: Application site erythema/flush	54.50	£43.82 - £65.18 (Normal)	
AE costs: Application site pruritus	54.50	£43.82 - £65.18 (Normal)	
AE costs: Headache	54.50	£43.82 - £65.18 (Normal)	
AE costs: Nausea	54.50	£43.82 - £65.18 (Normal)	
AE costs: Diarrhoea	54.50	£43.82 - £65.18 (Normal)	
AE costs: Gastro-oesophageal reflux/gastrointestinal discomfort/abdominal pain upper	54.50	£43.82 - £65.18 (Normal)	
AE costs: Asthenia/Somnolence	54.50	£43.82 - £65.18 (Normal)	
AE costs: Dizziness	54.50	£43.82 - £65.18 (Normal)	
AE costs: Blurred vision	54.50	£43.82 - £65.18 (Normal)	
AE costs: Urinary difficulty/frequent urination/urinary retention/bladder discomfort	54.50	£43.82 - £65.18 (Normal)	
AE costs: Injection site pain	9.17	£7.37 - £10.96 (Normal)	
AE costs: Injection site bleeding	9.17	£7.37 - £10.96 (Normal)	
AE costs: Non-axillary sweating/hyperhidrosis	1378.78	£1230.57 - £1830.54 (Normal)	
Treatment duration			
GPB 1% cream: Proportion of discontinuations 0-72 weeks	[redacted]	[redacted]	Section 3.2.3, Page 74-75
GPB 1% cream: Number of applications per week 2	[redacted]	[redacted]	

GPB 1% cream: Number of applications per week 4	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 6	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 8	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 10	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 12	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 14	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 16	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 18	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 20	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 22	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 24	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 26	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 28	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 30	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 32	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 34	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 36	[redacted]	[redacted]

GPB 1% cream: Number of applications per week 38	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 40	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 42	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 44	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 46	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 48	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 50	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 52	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 54	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 56	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 58	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 60	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 62	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 64	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 66	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 68	[redacted]	[redacted]
GPB 1% cream: Number of applications per week 70	[redacted]	[redacted]

GPB 1% cream: Number of applications per week 72	[redacted]	[redacted]	
Antimuscarinics: Proportion of discontinuations 0-26 weeks	[redacted]	[redacted]	
Botulinum toxin: Proportion of discontinuations 0-26 weeks	[redacted]	[redacted]	
Utilities			
Utilities HDSS=1	0.90	0.84 - 0.95 (Beta)	Section 3.4.5, Page 96
Utilities HDSS=2	0.85	0.52 - 1 (Beta)	
Utilities HDSS=3	0.80	0.44 - 0.99 (Beta)	
Utilities HDSS=4	0.69	0.25 - 0.98 (Beta)	
Utility decrement: Dry eye	-0.01	-0.011 - -0.0074 (Normal)	Section 3.4.5, Page 96
Utility decrement: Dry mouth	0.00	-0.0028 - -0.0019 (Normal)	
Utility decrement: Application site erythema/flush	0.00	-0.0007 - -0.0005 (Normal)	
Utility decrement: Application site pruritus	0.00	-0.0007 - -0.0005 (Normal)	
Utility decrement: Headache	-0.03	-0.0318 - -0.0214 (Normal)	
Utility decrement: Nausea	-0.05	-0.0612 - -0.0412 (Normal)	
Utility decrement: Diarrhoea	-0.05	-0.0612 - -0.0412 (Normal)	
Utility decrement: Gastro-oesophageal reflux/other GI disorders	-0.07	-0.0868 - -0.0583 (Normal)	
Utility decrement: Asthenia/Somnolence	-0.02	-0.0239 - -0.0161 (Normal)	
Utility decrement: Dizziness	-0.03	-0.0318 - -0.0214 (Normal)	

Utility decrement: Blurred vision	0.00	0 - 0 (Normal)
Utility decrement: Urinary difficulty/other renal or urinary disorder	-0.07	-0.0841 - -0.0566 (Normal)
Utility decrement: Injection site pain	0.00	-0.0048 - -0.0032 (Normal)
Utility decrement: Injection site bleeding	0.00	-0.0048 - -0.0032 (Normal)
Utility decrement: Non-axillary sweating/hyperhidrosis	-0.12	-0.1457 - -0.0979 (Normal)
AE duration: Dry eye	14.00	11.3 - 16.7 (Normal)
AE duration: Dry mouth	14.00	11.3 - 16.7 (Normal)
AE duration: Application site erythema/flush	14.00	11.3 - 16.7 (Normal)
AE duration: Application site pruritus	14.00	11.3 - 16.7 (Normal)
AE duration: Headache	14.00	11.3 - 16.7 (Normal)
AE duration: Nausea	14.00	11.3 - 16.7 (Normal)
AE duration: Diarrhoea	14.00	11.3 - 16.7 (Normal)
AE duration: Gastro-oesophageal reflux/other GI disorders	14.00	11.3 - 16.7 (Normal)
AE duration: Asthenia/Somnolence	14.00	11.3 - 16.7 (Normal)
AE duration: Dizziness	14.00	11.3 - 16.7 (Normal)
AE duration: Blurred vision	14.00	11.3 - 16.7 (Normal)
AE duration: Urinary difficulty/other renal or urinary disorder	14.00	11.3 - 16.7 (Normal)
AE duration: Injection site pain	2.40	1.9 - 2.9 (Normal)
AE duration: Injection site bleeding	2.40	1.9 - 2.9 (Normal)

AE duration: Non-axillary sweating/hyperhidrosis	14.00	11.3 - 16.7 (Normal)

Abbreviations: AE, adverse event, FAS, full analysis set; GI, gastrointestinal; GP, general practitioner; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; PPS, per-protocol set; U, units.

3.8.2 Assumptions

Table 47 details the key assumptions underpinning the economic model and the justification for these.

Table 47: Summary of assumptions applied in the economic model

Parameter	Base case	Justification
Treatment effect for GPB 1% cream beyond the 72 week trial period	For patients who remain on treatment beyond the 72-week Phase 3b trial period, the model conservatively assumes no further movement between HDSS health states.	While some individuals may experience a reduction in treatment effect over time, this is offset by the larger proportion of patients who continue to improve, as evidenced by an increase in those achieving ≥2-point improvements in HDSS scores between weeks 52 and 72 in the FASb population, and by the ongoing reduction in mean HDSS scores reported in Szeimies et al. (2022).[25] Therefore, the base case assumption is conservative as the overall HDSS change over time would likely be positive. A scenario analysis explores the potential impact of continued improvement beyond 72 weeks, based on these observed trends.
Transitions	The probability of improvements in HDSS score is assumed to be constant across HDSS health states.	This aligns with the available data and is a consistent approach across all comparators.
Antimuscarinics comparator	Comprises 35.4% propantheline bromide, 46.2% oxybutynin, and 18.5% oral GPB	Reflects the treatment options available in UK clinical practice (Section 3.2.3.2). The distribution reflects the feedback from the UK-based survey of dermatologists in Wade et al. (2017).[18]
Dose of antimuscarinics	Daily doses of 75 mg for propantheline bromide, 7.5 mg for oxybutynin, and 2 mg for oral GPB.	These doses align with the BNF and Schollhammer et al. (2015) for oxybutynin. A scenario analysis explores the impact of a daily dose of 12.5mg for oxybutynin.[26,47]
Efficacy for antimuscarinics	Bucher ITC based on data from the Phase 3a clinical trial for GPB 1% cream and Schollhammer et al. (2015).	It is assumed that there is a class effect for antimuscarinics and that the treatment effect of these

		medications vs. placebo can be based on the oxybutynin study reported in Schollhammer et al. (2015). This assumption aligns with assumptions made in the published ITC in a Centre for Reviews and Dissemination Health Technology Assessment (Wade et al. (2017)). A scenario analysis considers the impact of the OR estimated in Wade et al. (2017) for antimuscarinics vs. placebo informing the Bucher ITCs.
Transitions relating to antimuscarinics	For 1-2 HDSS improvement for antimuscarinics, the OR for the ≥1 HDSS improvement endpoint is assumed.	This assumption is required as data are unavailable for the 1-2 HDSS improvement endpoint for antimuscarinics.
Dose of botulinum toxin	50U of botulinum toxin per axilla (100U in total).	This is consistent with the SmPC for Botox, UK clinical expert input, and the clinical trial data used to inform efficacy in the base case.[12,14,27] Scenario analyses explore the impact of 75U per axilla (150U) and an average across 50U and 75U doses, varying the doses and the source of efficacy and safety data accordingly.
Botulinum toxin re-treatment frequency	Two procedures a year.	This assumption aligns with feedback from UK clinical experts and the literature: Bloudek et al. (2021) and Wade et al. (2017) assumed two procedures per year, Gibbons et al. (2015) assumed 2.1, and Isla-Tejera et al. (2013) allowed a maximum of two.[12,18,39,41,42] A scenario analysis explores the impact of 1.8 procedures per year based on the need for re-treatment following the end of the treatment effect at 201 days (201/365.25) reported in Lowe et al. (2007).[27]

Efficacy for botulinum toxin	Bucher ITC based on data from the Phase 3a clinical trial for GPB 1% cream and Lowe et al. (2007).	Lowe et al. (2007) reflects data aligned with the target population in this appraisal and reports on HDSS outcomes in a randomised comparison with placebo. A scenario analysis considers the impact of the OR estimated in Wade et al. (2017) for botulinum toxin vs. placebo informing the Bucher ITCs.
Transitions relating to botulinum toxin	The proportional difference between ≥1 and ≥2 HDSS improvement ORs estimated for antimuscarinics is used to estimate the OR for the ≥1 and 1-2 HDSS improvement endpoints for botulinum toxin.	This assumption is required as data are unavailable for the ≥1 and 1-2 HDSS improvement endpoints for botulinum toxin. The data from the Phase 3a GPB 1% cream clinical trial and Schollhammer et al. (2015) indicate that the response rates for a ≥1 HDSS improvement are much less than the ≥2 HDSS improvement – supporting the base case assumption. A scenario analysis explores the use of the ≥2 HDSS improvement OR across all endpoints for botulinum toxin vs. GPB 1% cream.
Efficacy related to re-treatments	The efficacy associated with subsequent botulinum toxin treatment is aligned with the initial treatment.	There is currently inconclusive evidence in the literature regarding whether the treatment effect of botulinum toxin changes with subsequent sessions for HH. Scenario analyses explore the use of the improved OR reported for the second session in Lowe et al. (2007), as well as scenarios assuming a 10% and 20% reduction in ORs from the initial treatment, applied to all subsequent botulinum toxin procedures.
Treatment waning for botulinum toxin	Its treatment effect is modelled based on peak efficacy at 4 weeks, followed by a decline to no effect by 6 months, at which point patients are assumed to return to baseline HDSS values.	The timepoint of 4 weeks is based on the available data from Lowe et al. (2007) informing the Bucher ITCs. The timepoint of 6 months is based on two procedures a year

		– as described above. Scenario analyses explore 8 and 12 week maximum efficacy timepoints.
HDSS score after discontinuation	Revert to baseline HDSS score.	This assumption is considered reflective of what would happen in UK clinical practice i.e., there is no sustained treatment benefit after discontinuation. This assumption aligns with the assumption made in Bloudek et al. (2021).[39]
Number of applications beyond 72 weeks for GPB 1% cream	Beyond 72 weeks, the model assumes the mean number of applications at 72 weeks for the rest of the model time horizon.	This aligns with the last data point from the Phase 3b clinical trial. The number of applications appears to stabilise across the long-term follow-up.
Discontinuation rate for GPB 1% cream	It is assumed that this discontinuation rate (0.95% per 2-week cycle) continues beyond the 72-week trial period and remains constant over the model time horizon.	A scenario analysis is conducted to assess the impact of increasing this long-term discontinuation rate by 10% and 20%, to explore the sensitivity of the model outcomes to this assumption.
Discontinuation rate for antimuscarinics	The data from Wolosker et al. (2014) inform the discontinuation rate per cycle which remains constant over the model time horizon.[56]	There are no treatment duration data in Schollhammer et al. (2015). Therefore, two observational studies are considered. Wolosker et al. (2014) focuses specifically on AHH, it is considered more aligned with the target population for this appraisal. Therefore, the discontinuation rate of 50.9% over 6 months is used in the economic model. A scenario analysis uses data from Millán-Cayetano et al. (2017).[57]
Discontinuation for botulinum toxin	It is assumed that all patients who formally discontinued in Lowe et al. (2007), along with half of those who completed the study without further treatment, are true discontinuers.	This assumption is required due to limited follow-up in Lowe et al. (2007), and the fact that some patients were still at the second procedure stage when the study ended. Therefore, data beyond the first procedure are incomplete. Scenario analyses are conducted where

		only formal discontinuations are considered and all discontinuations and those without further treatment are considered.
Utility value for HDSS=1	Assumed in line with the age- and gender-matched population.	This assumption aligns with the literature (Bloudek et al. (2021) and Wade et al. (2017)).[18,39]
AEs for antimuscarinics	It is assumed that the AEs reported in Schollhammer et al. (2015) reflect the side effect profile associated with antimuscarinics.	Since oxybutynin is an anticholinergic and the side effect profile is well established in this drug class, it is assumed that this profile extends to other oral antimuscarinics included in the comparator arm.
Monitoring frequency	All patients are monitored every 3-months for the first year, followed by annually.	Aligning with expectations in UK clinical practice.[12]
Care setting	For GPB 1% cream, it is assumed that 100% of administration and monitoring occurs in primary care. For antimuscarinics, it is assumed that 25% of patients are initiated in primary care, 25% in primary care following A&G, and 50% in secondary care. For botulinum toxin, it is assumed that 100% of administration and monitoring occurs in secondary care.	Aligned with expectations in UK clinical practice.
Subsequent therapies	For patients who discontinue GPB 1% cream and require further treatment, it is assumed they are referred to secondary care. Of these, 10% receive antimuscarinics and 90% receive botulinum toxin. For patients discontinuing antimuscarinics, it is assumed they are referred to secondary care. Of these, 10% receive a different antimuscarinic, 85% receive botulinum toxin, and 5% receive unlicensed GPB in secondary care. For those who discontinue botulinum	Aligned with expectations in UK clinical practice.

	toxin, it is assumed that 50% transition to antimuscarinics and 50% to unlicensed GPB.

Abbreviations: AE, adverse event; HDSS, Hyperhidrosis Disease Severity Score; HH, hyperhidrosis; ITC, indirect treatment comparison; OR, odds ratio; U, unit; UK, United Kingdom.

3.9 Base-case results

3.9.1 Base-case incremental cost-effectiveness analysis results

Table 48 presents the base case pairwise results vs. GPB 1% cream and Table 49 presents the incremental analysis. Table 50 presents the corresponding net health benefits (NHBs) vs. GPB 1% cream.

3.9.1.1 GPB 1% cream vs. antimuscarinics

In the base case analysis, GPB 1% cream generates [redacted] additional QALYs at a reduced cost of [redacted] compared to antimuscarinics. As it delivers greater health benefits at a lower overall cost, GPB 1% cream is considered dominant relative to antimuscarinics. The additional QALYs are primarily driven by patients remaining on GPB 1% cream for a longer duration, maintaining HDSS response over time. Furthermore, the utility decrement associated with AEs is lower for GPB 1% cream than for antimuscarinics. Although the acquisition and administration costs of GPB 1% cream are higher, these are offset by savings from fewer AEs and a reduced need for subsequent therapies, due to sustained treatment. The NHB is [redacted] at a willingness-to-pay (WTP) threshold of £20,000, and [redacted] at a threshold of £30,000. Corresponding net monetary benefits (NMBs) are [redacted] and [redacted], respectively.

3.9.1.2 GPB 1% cream vs. botulinum toxin

In the base case analysis, GPB 1% cream generates [redacted] additional QALYs at a reduced cost of [redacted] compared to botulinum toxin. As it delivers greater health benefits at a lower overall cost, GPB 1% cream is considered dominant relative to botulinum toxin. The additional QALYs are primarily driven by patients remaining on GPB 1% cream for a longer duration, maintaining HDSS response over time. Furthermore, the utility decrement associated with AEs is lower for GPB 1% cream than for botulinum toxin. Cost savings are demonstrated for GPB 1% cream across administration, AEs, and subsequent therapies compared to botulinum toxin. The NHB is [redacted] at a WTP threshold of £20,000, and [redacted] at a threshold of £30,000. Corresponding NMBs are [redacted] and [redacted], respectively.

Table 48: Base-case results vs. GPB 1% cream

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 49: Incremental analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 50: Net health benefit vs. GPB 1% cream

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

3.10 Exploring uncertainty

3.10.1 Probabilistic sensitivity analysis

The probabilistic sensitivity analysis (PSA) explores the joint uncertainty of all relevant model parameters and their impact on cost-effectiveness outcomes. This is achieved by randomly sampling values for each parameter from their respective probability distributions and re-estimating the ICER at each iteration. A total of 1,000 iterations were conducted. The results are illustrated using a scatterplot that maps incremental costs against incremental QALYs, providing a visual representation of the variability in outcomes.

A corresponding cost-effectiveness acceptability curve (CEAC) is presented to show the probability that GPB 1% cream is cost-effective at various WTP thresholds. The parameter inputs, distributions, and ranges used in the PSA are detailed in Table 46.

The proportion of PSA iterations where GPB 1% cream is considered cost-effective is [redacted] at a £20,000/QALY threshold. The CEAC is shown in Figure 10.

Figure 10: CEAC

[redacted]

Abbreviations: CEAC, cost-effectiveness acceptability curve; GPB, glycopyrronium bromide.

3.10.1.1 GPB 1% cream vs. antimuscarinics

The PSA results indicate an average incremental cost of [redacted] and an average incremental QALY gain of [redacted] for GPB 1% cream compared to antimuscarinics. These results are consistent with the deterministic analysis, confirming that GPB 1% cream is dominant (i.e., more effective and less costly). This consistency is visually supported by the overlap of the deterministic and probabilistic base case markers in the cost-effectiveness plane (Figure 11).

Figure 11: Cost-effectiveness plane (1,000 iterations) | GPB 1% cream vs. antimuscarinics

Abbreviations: GPB, glycopyrronium bromide; QALY, quality adjusted life year; WTP, willingness-to-pay.

3.10.1.2 GPB 1% cream vs. botulinum toxin

For the comparison with botulinum toxin, the PSA shows an average incremental cost of [redacted] and an average incremental QALY gain of [redacted] for GPB 1% cream. Again, the probabilistic results are aligned with the deterministic findings, indicating dominance of GPB 1% cream. This is further evidenced by the overlap in the deterministic and probabilistic results on the cost-effectiveness plane (Figure 12).

Figure 12: Cost-effectiveness plane (1,000 iterations) | GPB 1% cream vs. botulinum toxin

Abbreviations: GPB, glycopyrronium bromide; QALY, quality adjusted life year; WTP, willingness-to-pay.

3.10.2 Deterministic sensitivity analysis

Parameter uncertainty was tested using univariate sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible range determined by the 95% confidence intervals (Table 46).

3.10.2.1 GPB 1% cream vs. antimuscarinics

Results for the ten most influential parameters for GPB 1% cream vs. antimuscarinics are shown in Table 51 and depicted in a tornado diagram in Figure 13 and

Figure 14 based on the ICER and a NMB with a WTP of £20,000, respectively.

Across all parameter variations within their respective lower and upper bounds, GPB 1% cream remains dominant compared to antimuscarinics, except in two scenarios: when the upper bound of the utility value for the HDSS=4 health state and the lower bound for the HDSS=2 health state are applied.

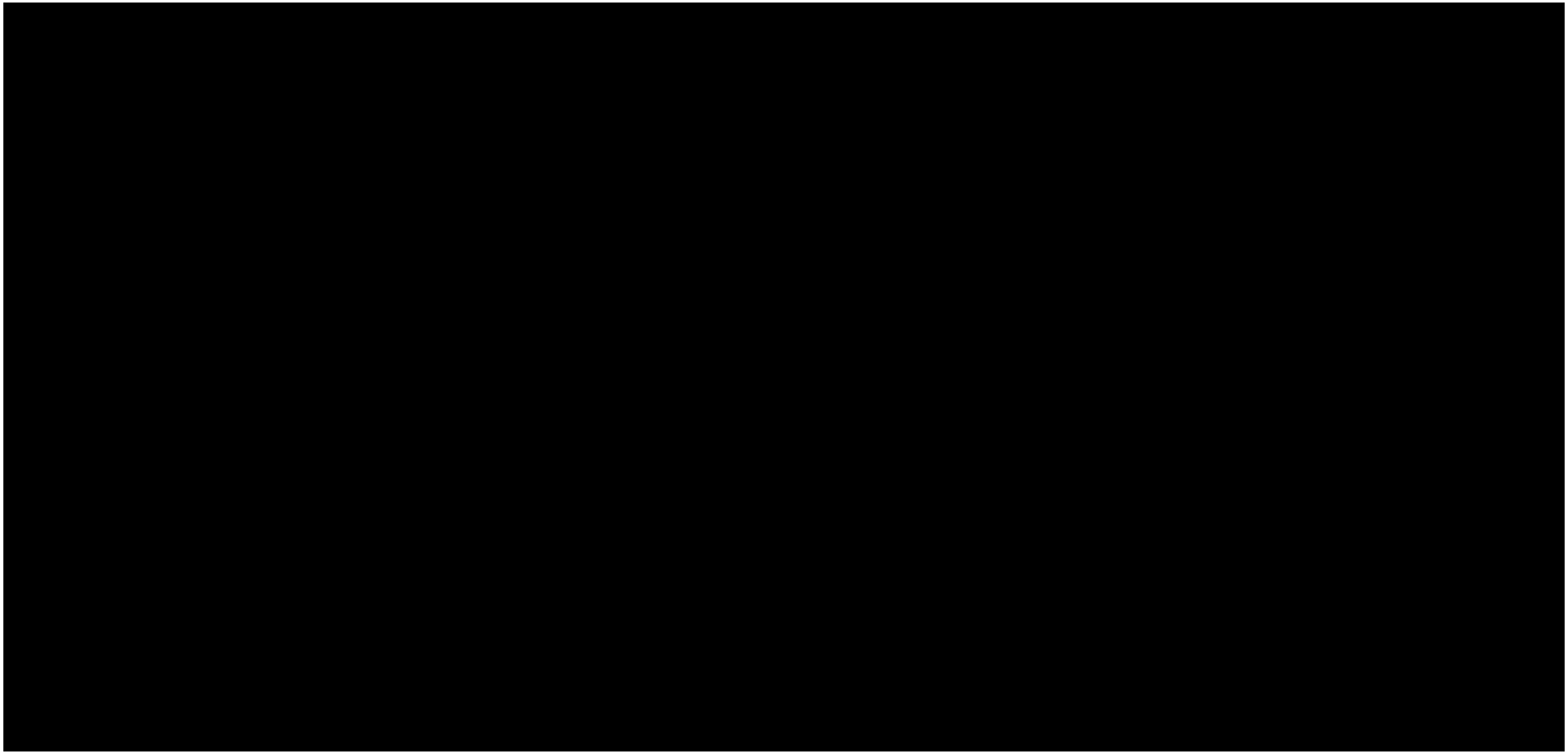
In these scenarios, GPB 1% cream appears less effective and less costly than antimuscarinics, placing the ICER in the south-west quadrant of the cost-effectiveness plane. However, these results should be interpreted with caution. For example, setting the HDSS=2 utility value to the lower bound ([redacted]) produces a utility that is lower than those of the more severe HDSS=3 and HDSS=4 health states, which is not clinically plausible. As more severe health states are expected to correspond with lower HRQoL, this contradicts clinical expectations. Additionally, the confidence intervals for these utility values were derived from published literature and are associated with large standard deviations. As a result, the sensitivity analyses incorporate wide parameter ranges.

Table 51: Top ten parameters impacting the ICER (one-way sensitivity analysis) | GPB 1% cream vs. antimuscarinics

Parameter	Lower bound	Upper bound	Difference
Utilities HDSS=4	[redacted]	[redacted]	[redacted]
Antimuscarinics: 2-week proportion of AEs, Non-axillary sweating/hyperhidrosis	[redacted]	[redacted]	[redacted]
Utilities HDSS=3	[redacted]	[redacted]	[redacted]
Utilities HDSS=2	[redacted]	[redacted]	[redacted]
Antimuscarinics: Proportion of discontinuations 0-26 weeks	[redacted]	[redacted]	[redacted]
GPB 1% cream: Proportion of discontinuations 0-72 weeks	[redacted]	[redacted]	[redacted]
Antimuscarinics: proportion unlicensed GPB (secondary care) subsequent therapy	[redacted]	[redacted]	[redacted]
Antimuscarinics: proportion Botulinum toxin (secondary care) subsequent therapy	[redacted]	[redacted]	[redacted]
GPB 1% cream: proportion Botulinum toxin (secondary care) subsequent therapy	[redacted]	[redacted]	[redacted]
Propantheline bromide: cost per pack	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; ICER, incremental cost-effectiveness ratio.

Figure 13: Tornado plot, ICER (one-way sensitivity analysis) | GPB 1% cream vs. antimuscarinics



Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; ICER, incremental cost-effectiveness ratio.

Figure 14: Tornado plot, NMB at a WTP of £20,000 (one-way sensitivity analysis) | GPB 1% cream vs. antimuscarinics

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; NMB, net monetary benefit; WTP, willingness-to-pay.

3.10.2.2 GPB 1% cream vs. botulinum toxin

Results for the ten most influential parameters for GPB 1% cream vs. botulinum toxin are shown in Table 52 and depicted in a tornado diagram in Figure 15 and Figure 16 based on the ICER and a NMB with a WTP of £20,000, respectively.

Across all parameter variations within their respective lower and upper bounds, GPB 1% cream remains dominant compared to botulinum toxin, except in two scenarios: when the upper bound of the utility value for the HDSS=4 health state and the lower bound for the HDSS=2 health state are applied. The same parameters influencing the interpretation of results in the comparison between GPB 1% cream and antimuscarinics also apply to the comparison with botulinum toxin, and the same caveats remain relevant.

Table 52: Top ten parameters impacting the ICER (one-way sensitivity analysis) | GPB 1% cream vs. botulinum toxin

Parameter	Lower bound	Upper bound	Difference
Utilities HDSS=4	[redacted]	[redacted]	[redacted]
Utilities HDSS=3	[redacted]	[redacted]	[redacted]
Utilities HDSS=2	[redacted]	[redacted]	[redacted]
Subsequent therapy costs: unlicensed GPB (secondary care)	[redacted]	[redacted]	[redacted]
Botulinum toxin: proportion unlicensed GPB (secondary care) subsequent therapy	[redacted]	[redacted]	[redacted]
Botulinum toxin: Proportion of discontinuations 0-26 weeks	[redacted]	[redacted]	[redacted]
Utilities HDSS=1	[redacted]	[redacted]	[redacted]
Subsequent therapy costs: Botulinum toxin (secondary care)	[redacted]	[redacted]	[redacted]
Unlicensed GPB: cost per tube	[redacted]	[redacted]	[redacted]
Number of Botulinum toxin procedures per year	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; ICER, incremental cost-effectiveness ratio.

Figure 15: Tornado plot, ICER (one-way sensitivity analysis) | GPB 1% cream vs. botulinum toxin

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; ICER, incremental cost-effectiveness ratio.

Figure 16: Tornado plot, NMB at a WTP of £20,000 (one-way sensitivity analysis) | GPB 1% cream vs. botulinum toxin

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; NMB, net monetary benefit; WTP, willingness-to-pay.

3.10.3 Scenario analysis

Scenario analyses were conducted to assess structural uncertainty within the economic model. A comprehensive list of the scenarios evaluated is provided in Table 53. The corresponding results from the deterministic analyses for GPB 1% cream vs. antimuscarinics are shown in Table 54 and Table 55 for the ICER and NMB with a WTP of £20,000, respectively. For GPB 1% cream vs. botulinum toxin these are shown in Table 57 and Table 58, respectively.

Given the number of scenarios explored, probabilistic analyses were performed for the scenarios that had the greatest impact on cost-effectiveness outcomes in the deterministic results. These probabilistic scenario analyses were conducted using 1,000 PSA iterations per scenario, following the same methodology as the base case PSA described in Section 3.10.1.

The probabilistic scenario analyses are detailed below:

- **GPB 1% cream efficacy source:** Utilising the PPSb population for GPB 1% cream efficacy data, compared with the FASb population in the base case.
- **Assumptions around the ongoing treatment benefit for GPB 1% cream beyond the 72 week trial period:** Assuming the observed increase in the proportion of patients achieving a ≥2 HDSS score improvement between weeks 52 and 72 for all patients remaining on treatment with GPB 1% cream beyond 72 weeks, compared with no HDSS improvement after 72 weeks in the base case.
- **Discontinuation rate for antimuscarinics:** Applying alternative discontinuation data from Millán-Cayetano et al. (2017), compared with Wolosker et al. (2014) in the base case.
- **Discontinuation rate for botulinum toxin:** Assuming only formal discontinuations from Lowe et al. (2007), compared with assuming these and 50% of those who did not receive another procedure within the study follow-up in the base case.

The results from these probabilistic analyses are presented in Table 56 for the comparison between GPB 1% cream and antimuscarinics, and in Table 59 for the comparison between GPB 1% cream and botulinum toxin.

Across all deterministic and probabilistic scenarios, GPB 1% cream remains cost-effective i.e., the NMB remains positive at a WTP threshold of £20,000. Based on the probabilistic scenarios:

- **GPB 1% cream efficacy source:** Using the efficacy from the PPSb population for GPB 1% cream results in improved outcomes, with the probabilistic NMB increasing by +27.9% compared to antimuscarinics and +33.1% compared to botulinum toxin. This is attributed to improved outcomes observed in the PPSb population for GPB 1% cream relative to the FASb population. This demonstrates that the base case may be conservative. Nevertheless, the base case uses the FASb population as this is likely to be more reflective of real-world UK clinical practice.

- **Assumptions around the ongoing treatment benefit for GPB 1% cream beyond the 72-week trial period:** Assuming a continued treatment benefit of GPB 1% cream beyond the 72-week follow-up period of the Phase 3b trial leads to improved outcomes, with probabilistic NMBs increasing by 25.3% compared to antimuscarinics and 20.3% compared to botulinum toxin. Phase 3b trial data support this assumption, showing continued improvements between weeks 52 and 72—including an increased proportion of patients achieving HDSS = 1, ≥2-point HDSS score improvements, and a higher mean HDSS score. As such, the base case is highly conservative, given that patients remaining on treatment are likely to experience ongoing clinical benefit.
- **Discontinuation rate for antimuscarinics:** Applying discontinuation rates from Millán-Cayetano et al. (2017) results in improved outcomes for GPB 1% cream, with probabilistic NMBs increasing by 47.2% compared to antimuscarinics and by 33.4% compared to botulinum toxin. The lower discontinuation rate for antimuscarinics increases associated drug acquisition, administration, and AE costs, which offsets the gains in QALYs and ultimately benefits the relative cost-effectiveness of GPB 1% cream. This suggests that the discontinuation data used in the base case may be conservative. However, the higher discontinuation rate from Wolosker et al. (2014) is considered more representative of real-world clinical practice, supporting its use in the base case analysis.
- **Discontinuation rate for botulinum toxin:** Assuming only formal discontinuations from Lowe et al. (2007) lowers the discontinuation rate for botulinum toxin, resulting in increased costs and improved efficacy. In the comparison with antimuscarinics, the rise in costs leads to a higher probabilistic NMB for GPB 1% cream, increasing by +5.3%. This is driven by the higher cost of subsequent botulinum toxin treatments and earlier and a higher rate of transitions to subsequent therapies in the antimuscarinics arm compared to GPB 1% cream. In the comparison with botulinum toxin, while the costs of botulinum toxin increase, the associated efficacy improvement outweighs these gains, resulting in a -7.9% reduction in probabilistic NMB. Nonetheless, the NMB remains positive, indicating that GPB 1% cream remains a cost-effective option under this scenario.

In conclusion, GPB 1% cream demonstrates consistent cost-effectiveness across various deterministic and probabilistic scenarios, maintaining a positive NMB at a WTP threshold of £20,000.

Table 53: Scenario analyses

	Base case	Scenario	Rationale
Time horizon	Lifetime (65 years)	20 years 40 years 60 years	A lifetime horizon aligns with NICE guidance and captures long-term differences in outcomes.[46] Shorter horizons are explored in scenario analyses.
Half cycle correction	Included	Excluded	To test the impact of removing the correction for cycle length.
Discount rates	3.5% costs and QALYs	0.0% costs and QALYs	To evaluate the impact of no discounting.
Baseline characteristics for age and gender	FASb	FASa PPSb	FASb aligns with the primary efficacy data for GPB 1% cream. Other populations are explored for sensitivity.
Efficacy for GPB 1% cream in model	FASb	PPSb	The FASb population likely better reflects how GPB 1% cream would be used in UK clinical practice. Additionally, more data are available for the FASb population compared to the PPSb population. This is a conservative assumption as the treatment effect for GPB 1% cream vs. placebo is larger in the PPSb population. To explore the impact of this, a scenario uses the data from the PPSb population.
Treatment effect for patients continuing to receive GPB 1% cream beyond the 72 week trial period	Assumed HDSS state maintained for all patients continuing to receive GPB 1% cream beyond trial period	Probability of improvement in HDSS [redacted]% per 2-week cycle (calculated from difference in week 52 and week 72 ≥2 HDSS responders)	While some individuals may experience a reduction in treatment effect over time, this is offset by the larger proportion of patients who continue to improve, as evidenced by an increase in those achieving ≥2-point improvements in HDSS scores between weeks 52 and 72 in the FASb population, and by the ongoing reduction in mean HDSS scores reported in Szeimies et al. (2022).[25] Therefore, the base case assumption is conservative as the

			overall HDSS change over time would likely be positive. A scenario analysis explores the potential impact of continued improvement beyond 72 weeks, based on these observed trends.
Relative efficacy of antimuscarinics vs. GPB 1% cream	Based on FASa (GPB 1% cream) and Schollhammer et al. (2015) (antimuscarinics)	PPSa Wade et al. (2017)	The FASa population likely better reflects how GPB 1% cream would be used in UK clinical practice. This is a conservative assumption as the treatment effect for GPB 1% cream vs. placebo is larger in the PPSa population. To explore the impact of this, a scenario uses the data from the PPSa population. Schollhammer et al. (2015) report outcomes for oxybutynin which is an antimuscarinic which is used in UK clinical practice.[26] Whilst Wade et al. (2017) assumed that all medications have a similar efficacy vs. placebo, the data informing their NMA came from studies of medications either not frequently used or unavailable in UK clinical practice. However, to explore the impact of this, a scenario uses the output from Wade et al. (2017).[18]
Relative efficacy of botulinum toxin vs. GPB 1% cream	Based on FASa (GPB 1% cream), Lowe et al. (2007) (botulinum toxin), and assuming the same proportional difference between ≥1 and ≥2 HDSS score improvement outcomes for antimuscarinics	PPSa Wade et al. (2017) Assuming the relative efficacy for a ≥1 HDSS score improvement is the same as a ≥2 HDSS score improvement	The FASa population likely better reflects how GPB 1% cream would be used in UK clinical practice. This is a conservative assumption as the treatment effect for GPB 1% cream vs. placebo is larger in the PPSa population. To explore the impact of this, a scenario uses the data from the PPSa population. Lowe et al. (2007) report outcomes for botulinum toxin in a population generalisable to UK clinical practice.[27] Whilst Wade et al. (2017) considered an additional study in their NMA reflecting outcomes in a Japanese population, which was not considered generalisable to UK clinical practice. However, to explore the impact of this, a scenario uses the output from Wade et al. (2017).

			There are no data in the literature for the effects of botulinum toxin vs. placebo on ≥1 HDSS score improvements (only ≥2 HDSS score improvements). In the base case, it is assumed that the proportional difference in these response definitions observed for antimuscarinics is applied to botulinum toxin. This is supported by the evidence available for GPB 1% cream and antimuscarinics which show that the relative efficacy are not consistent for these endpoints. However, to explore this, a scenario assumes the same relative efficacy for ≥1 and ≥2 HDSS score improvements.
Dose of botulinum toxin	100U (50U per axilla)	150U	The base case dose of 100U aligns with feedback from UK clinical experts.[12] Scenario analyses explore the impact of alternative doses for botulinum toxin.
Relative efficacy of botulinum toxin subsequent treatments vs. GPB 1% cream	Assumed the same efficacy as initial treatment	Combined Lowe et al. (2007) 10% lower OR 20% lower OR	The data on the relative efficacy of botulinum toxin following multiple procedures is inconclusive. In the base case, subsequent procedures are assumed to have the same relative efficacy as the initial procedure. Scenario analyses explore improved efficacy for subsequent procedures (as in Lowe et al. (2007)) and worse efficacy for subsequent procedures.
Maximum botulinum toxin treatment effect	4 weeks	8 weeks 12 weeks	The base case assumes that the maximum efficacy for botulinum toxin is reached after 4 weeks – this is consistent with the data points from Lowe et al. (2007). Scenario analyses explore the impact of 8 and 12 weeks.
Number of botulinum procedures per year	2	1.8	This assumption aligns with feedback from UK clinical experts and the literature: Bloudek et al. (2021) and Wade et al. (2017) assumed two procedures per year, Gibbons et al. (2015) assumed 2.1, and Isla-Tejera et al. (2013) allowed a maximum of two.[12,18,39,41,42] A scenario analysis explores the impact of 1.8 procedures per year based on the need for re-treatment following the end of the treatment effect at 201 days (201/365.25) reported in Lowe et al. (2007).

Cost of propantheline bromide	£103.52	£20.74	Prices on the BNF range from £20.74 to £195.14. Due to recent supply shortages of the lower-cost formulation, higher-cost packs are now more commonly used in UK clinical practice. Accordingly, the higher cost of £103.52 is used in the base case to reflect current UK clinical practice, with a scenario analysis assessing the impact of the lower £20.74 cost.[47]
Dose per day of oxybutynin	7.5mg	12.5mg	The base case dose of 7.5mg per day aligns with Schollhammer et al. (2015). A scenario analysis explores the dose assumed for oxybutynin in Wade et al. (2017), which aligns with the midpoint from their clinician survey.
Dose intensity of antimuscarinics	100%	[redacted]%	In the absence of dose intensity data, it is assumed that 100% of the dose is used (or wasted) for oral antimuscarinics. A scenario explores the impact of assuming the same dose intensity as GPB 1% cream.
Discontinuation rate for GPB 1% cream beyond the trial period	[redacted]%	Increased rate by 10% Increased rate by 20%	It is assumed that this discontinuation rate ([redacted]% per 2-week cycle) continues beyond the 72-week trial period and remains constant over the model time horizon. In absence of longer term data, scenario analyses explore increases of 10% and 20% to this rate.
Discontinuation rate for antimuscarinics	Wolosker et al. (2014)	Millan-Cayetano et al. (2017)	There are no treatment duration data in Schollhammer et al. (2015). Therefore, two observational studies are considered. Wolosker et al. (2014) focuses specifically on AHH, it is considered more aligned with the target population for this appraisal.[68] Therefore, the discontinuation rate of 50.9% over 6 months is used in the economic model. A scenario analysis uses data from Millán-Cayetano et al. (2017)[57].
Discontinuation rate for botulinum toxin	Assumed those who discontinued and half of the patients who did not receive another	Only those who formally discontinued Those who formally discontinued and those	This assumption is required due to limited follow-up in Lowe et al. (2007), and the fact that some patients were still at the second procedure stage when the study ended. Therefore, data beyond the first procedure are incomplete. Scenario analyses are conducted where only formal discontinuations

	treatment during follow-up	who did not receive another treatment during follow-up	are considered and all discontinuations and those without further treatment are considered.

Abbreviations: BNF, British National Formulary; FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; GPB, glycopyrronium bromide; PPS, per-protocol set; QALY, quality adjusted life year.

3.10.3.1 GPB 1% cream vs. antimuscarinics

Table 54: Deterministic scenario analyses (ICER) | GPB 1% cream vs. antimuscarinics

Scenario name	ICER	% change from base case
Base case	[redacted]	NA
Time horizon: 20-years	[redacted]	2.3%
Time horizon: 40-years	[redacted]	0.0%
Time horizon: 60-years	[redacted]	0.0%
Half cycle correction: excluded	[redacted]	7.9%
Discount rate: 0% costs and 0% outcomes	[redacted]	-71.1%
Baseline characteristics: FASa	[redacted]	1.4%
Baseline characteristics: PPSb	[redacted]	0.6%
Baseline GPB 1% cream efficacy: PPSb	[redacted]	-23.2%
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	-22.8%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on PPSa	[redacted]	-1.1%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on Wade et al. (2017)	[redacted]	-0.9%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on PPSa	[redacted]	0.0%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on Wade et al. (2017)	[redacted]	0.0%
Relative efficacy of GPB 1% cream vs. botulinum toxin ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	0.0%
Dose of botulinum toxin assumed 150U	[redacted]	5.1%
Dose of botulinum toxin assumed combined of 100U and 150U	[redacted]	2.6%
Relative efficacy for 2+ botulinum toxin procedures based on Lowe et al. (2007)	[redacted]	0.0%

Relative efficacy for 2+ botulinum toxin procedures based on a 10% reduction in OR	[redacted]	0.0%
Relative efficacy for 2+ botulinum toxin procedures based on a 20% reduction in OR	[redacted]	0.0%
Maximum botulinum toxin efficacy achieved at week 8	[redacted]	0.0%
Maximum botulinum toxin efficacy achieved at week 12	[redacted]	0.0%
1.8 botulinum procedures per year	[redacted]	0.2%
Cost of propantheline bromide of £20.74	[redacted]	-83.9%
Dose per day of oxybutynin of 12.5mg	[redacted]	1.0%
Dose intensity for oral antimuscarinics assumed equal to GPB 1% cream	[redacted]	-45.0%
Increase in discontinuation rate with GPB 1% cream of 10%	[redacted]	42.9%
Increase in discontinuation rate with GPB 1% cream of 20%	[redacted]	85.5%
Source of discontinuation for antimuscarinics from Millan-Cayetano et al. (2017)	[redacted]	5771.5%
Discontinuation for botulinum toxin assumed as only those who were formally discontinued	[redacted]	11.9%
Discontinuation for botulinum toxin assumed as those who were formally discontinued and no further treatment	[redacted]	-2.3%

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; GPB, glycopyrronium bromide; NMB, net monetary benefit; PPS, per-protocol set; WTP, willingness-to-pay.

Table 55: Deterministic scenario analyses (NMB based on a £20,000 WTP) | GPB 1% cream vs. antimuscarinics

Scenario name	NMB	% change from base case
Base case	[redacted]	NA
Time horizon: 20-years	[redacted]	-0.2%
Time horizon: 40-years	[redacted]	0.0%
Time horizon: 60-years	[redacted]	0.0%
Half cycle correction: excluded	[redacted]	0.9%

Discount rate: 0% costs and 0% outcomes	[redacted]	6.7%
Baseline characteristics: FASa	[redacted]	-0.8%
Baseline characteristics: PPSb	[redacted]	-0.3%
Baseline GPB 1% cream efficacy: PPSb	[redacted]	26.8%
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	26.3%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on PPSa	[redacted]	1.0%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on Wade et al. (2017)	[redacted]	0.8%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on PPSa	[redacted]	0.0%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on Wade et al. (2017)	[redacted]	0.0%
Relative efficacy of GPB 1% cream vs. botulinum toxin ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	0.0%
Dose of botulinum toxin assumed 150U	[redacted]	0.6%
Dose of botulinum toxin assumed combined of 100U and 150U	[redacted]	0.3%
Relative efficacy for 2+ botulinum toxin procedures based on Lowe et al. (2007)	[redacted]	0.0%
Relative efficacy for 2+ botulinum toxin procedures based on a 10% reduction in OR	[redacted]	0.0%
Relative efficacy for 2+ botulinum toxin procedures based on a 20% reduction in OR	[redacted]	0.0%
Maximum botulinum toxin efficacy achieved at week 8	[redacted]	0.0%
Maximum botulinum toxin efficacy achieved at week 12	[redacted]	0.0%
1.8 botulinum procedures per year	[redacted]	0.0%
Cost of propantheline bromide of £20.74	[redacted]	-9.3%
Dose per day of oxybutynin of 12.5mg	[redacted]	0.1%

Dose intensity for oral antimuscarinics assumed equal to GPB 1% cream	[redacted]	-5.0%
Increase in discontinuation rate with GPB 1% cream of 10%	[redacted]	-3.2%
Increase in discontinuation rate with GPB 1% cream of 20%	[redacted]	-5.9%
Source of discontinuation for antimuscarinics from Millan-Cayetano et al. (2017)	[redacted]	-9.9%
Discontinuation for botulinum toxin assumed as only those who were formally discontinued	[redacted]	1.3%
Discontinuation for botulinum toxin assumed as those who were formally discontinued and no further treatment	[redacted]	-0.3%

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; GPB, glycopyrronium bromide; NMB, net monetary benefit; PPS, per-protocol set; WTP, willingness-to-pay.

Table 56: Probabilistic scenario analyses | GPB 1% cream vs. antimuscarinics

	ICER	% change from base case	NMB, £20,000 WTP threshold	% change from base case
Probabilistic base case	[redacted]	NA	[redacted]	NA
Baseline GPB 1% cream efficacy: PPSb	[redacted]	-25.7%	[redacted]	+27.9%
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	-23.7%	[redacted]	+25.3%
Source of discontinuation for antimuscarinics from Millan-Cayetano et al. (2017)	[redacted]	3630.2%	[redacted]	+47.2%
Discontinuation for botulinum toxin assumed as only those who were formally discontinued	[redacted]	0.0%	[redacted]	+5.3%

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; ICER, incremental cost-effectiveness ratio; GPB, glycopyrronium bromide; NMB, net monetary benefit; PPS, per-protocol set; WTP, willingness-to-pay.

3.10.3.2 GPB 1% cream vs. botulinum toxin

Table 57: Deterministic scenario analyses (ICER) | GPB 1% cream vs. botulinum toxin

Scenario name	ICER	% change from base case
Base case	[redacted]	NA
Time horizon: 20-years	[redacted]	0.4%
Time horizon: 40-years	[redacted]	0.0%
Time horizon: 60-years	[redacted]	0.0%
Half cycle correction: excluded	[redacted]	1.3%
Discount rate: 0% costs and 0% outcomes	[redacted]	-22.6%
Baseline characteristics: FASa	[redacted]	1.0%
Baseline characteristics: PPSb	[redacted]	0.4%
Baseline GPB 1% cream efficacy: PPSb	[redacted]	-31.6%
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	-22.0%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on PPSa	[redacted]	1.4%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on Wade et al. (2017)	[redacted]	4.6%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on PPSa	[redacted]	-2.6%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on Wade et al. (2017)	[redacted]	0.3%
Relative efficacy of GPB 1% cream vs. botulinum toxin ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	4.6%
Dose of botulinum toxin assumed 150U	[redacted]	4.9%
Dose of botulinum toxin assumed combined of 100U and 150U	[redacted]	2.5%
Relative efficacy for 2+ botulinum toxin procedures based on Lowe et al. (2007)	[redacted]	4.6%

Relative efficacy for 2+ botulinum toxin procedures based on a 10% reduction in OR	[redacted]	-0.8%
Relative efficacy for 2+ botulinum toxin procedures based on a 20% reduction in OR	[redacted]	-1.8%
Maximum botulinum toxin efficacy achieved at week 8	[redacted]	8.5%
Maximum botulinum toxin efficacy achieved at week 12	[redacted]	15.3%
1.8 botulinum procedures per year	[redacted]	4.7%
Cost of propantheline bromide of £20.74	[redacted]	-8.2%
Dose per day of oxybutynin of 12.5mg	[redacted]	0.1%
Dose intensity for oral antimuscarinics assumed equal to GPB 1% cream	[redacted]	-4.4%
Increase in discontinuation rate with GPB 1% cream of 10%	[redacted]	11.2%
Increase in discontinuation rate with GPB 1% cream of 20%	[redacted]	22.3%
Source of discontinuation for antimuscarinics from Millan-Cayetano et al. (2017)	[redacted]	59.3%
Discontinuation for botulinum toxin assumed as only those who were formally discontinued	[redacted]	398.0%
Discontinuation for botulinum toxin assumed as those who were formally discontinued and no further treatment	[redacted]	-35.0%

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; GPB, glycopyrronium bromide; NMB, net monetary benefit; PPS, per-protocol set; WTP, willingness-to-pay.

Table 58: Deterministic scenario analyses (NMB based on a £20,000 WTP) | GPB 1% cream vs. botulinum toxin

Scenario name	NMB	% change from base case
Base case	[redacted]	NA
Time horizon: 20-years	[redacted]	-0.3%
Time horizon: 40-years	[redacted]	0.0%
Time horizon: 60-years	[redacted]	0.0%
Half cycle correction: excluded	[redacted]	0.4%

Discount rate: 0% costs and 0% outcomes	[redacted]	6.0%
Baseline characteristics: FASa	[redacted]	-0.7%
Baseline characteristics: PPSb	[redacted]	-0.3%
Baseline GPB 1% cream efficacy: PPSb	[redacted]	30.7%
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	18.8%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on PPSa	[redacted]	-1.0%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on Wade et al. (2017)	[redacted]	-2.9%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on PPSa	[redacted]	1.8%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on Wade et al. (2017)	[redacted]	-0.2%
Relative efficacy of GPB 1% cream vs. botulinum toxin ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	-2.9%
Dose of botulinum toxin assumed 150U	[redacted]	2.1%
Dose of botulinum toxin assumed combined of 100U and 150U	[redacted]	1.0%
Relative efficacy for 2+ botulinum toxin procedures based on Lowe et al. (2007)	[redacted]	-2.9%
Relative efficacy for 2+ botulinum toxin procedures based on a 10% reduction in OR	[redacted]	0.6%
Relative efficacy for 2+ botulinum toxin procedures based on a 20% reduction in OR	[redacted]	1.2%
Maximum botulinum toxin efficacy achieved at week 8	[redacted]	-5.2%
Maximum botulinum toxin efficacy achieved at week 12	[redacted]	-8.8%
1.8 botulinum procedures per year	[redacted]	-1.5%
Cost of propantheline bromide of £20.74	[redacted]	-2.7%
Dose per day of oxybutynin of 12.5mg	[redacted]	0.0%

Dose intensity for oral antimuscarinics assumed equal to GPB 1% cream	[redacted]	-1.5%
Increase in discontinuation rate with GPB 1% cream of 10%	[redacted]	-3.8%
Increase in discontinuation rate with GPB 1% cream of 20%	[redacted]	-7.0%
Source of discontinuation for antimuscarinics from Millan-Cayetano et al. (2017)	[redacted]	19.8%
Discontinuation for botulinum toxin assumed as only those who were formally discontinued	[redacted]	-12.5%
Discontinuation for botulinum toxin assumed as those who were formally discontinued and no further treatment	[redacted]	0.9%

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; GPB, glycopyrronium bromide; NMB, net monetary benefit; PPS, per-protocol set; WTP, willingness-to-pay.

Table 59: Probabilistic scenario analyses | GPB 1% cream vs. botulinum toxin

	ICER	% change from base case	NMB, £20,000 WTP threshold	% change from base case
Probabilistic base case	[redacted]	NA	[redacted]	NA
Baseline GPB 1% cream efficacy: PPSb	[redacted]	-33.4%	[redacted]	+33.1%
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	-23.6%	[redacted]	+20.3%
Source of discontinuation for antimuscarinics from Millan-Cayetano et al. (2017)	[redacted]	110.8%	[redacted]	+33.4%
Discontinuation for botulinum toxin assumed as only those who were formally discontinued	[redacted]	300.9%	[redacted]	-7.9%

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; ICER, incremental cost-effectiveness ratio; GPB, glycopyrronium bromide; NMB, net monetary benefit; PPS, per-protocol set; WTP, willingness-to-pay.

3.11 Benefits not captured in the QALY calculation

Beyond the clinical and economic outcomes captured in the model, GPB 1% cream offers several important societal benefits. Its convenience as a topical treatment, combined with a favourable safety profile, allows it to be prescribed and monitored entirely within the primary care setting. This ease of use translates into meaningful improvements in HRQoL that are not fully captured by health state utility values or AE decrements alone.

Primary care prescribing enhances accessibility. GP practices are typically closer to patients' homes, reducing travel time, minimising disruption to work or daily life, and supporting more equitable access - factors that are particularly important in PAHH, which often affects individuals of working age. Appointments are also often easier to obtain in primary care than in secondary care, making it less likely that patients will be lost to follow-up or face delays in ongoing treatment.

Compared with oral antimuscarinics, GPB 1% cream is safer, more manageable, and may be preferred by patients who are reluctant to take oral medications. GPs may feel more confident prescribing it following failure of aluminium-based antiperspirants, without needing A&G or referral to specialist care. In contrast, a significant proportion of antimuscarinic use still occurs in secondary care, requiring patients to attend hospital-based appointments - although efforts to shift prescribing to primary care are ongoing.

The AE profile reflected in Schollhammer et al. (2015), and hence in the model, is likely to underrepresent the AE burden associated with antimuscarinics in clinical practice, as the study only observed patients over a 6 week period. This short duration may miss the onset of longer-term or cumulative side effects such as dry eye, which is noted in the oxybutynin SmPC but not reported in Schollhammer et al. (2015). As such, the model may underestimate the true AE burden of these treatments.

Relative to botulinum toxin, GPB 1% cream is substantially more convenient. Botulinum toxin requires regular, scheduled procedures in specialist settings, which can be time-consuming and logistically burdensome for patients.

3.12 Validation

3.12.1 Internal validation of cost-effectiveness analysis

An internal quality assurance review of the electronic model was carried out by an independent health economics expert who was not involved in its development. The review followed a standardised checklist, drawing on guidance from Drummond et al. (1996), Phillips et al. (2004), and the NICE reference case.[46,69,70]

The assessment focused on verifying the accuracy and transparency of model calculations and functionality. In addition, the reviewer provided feedback on the appropriateness of the modelling approach and flagged any base-case settings or assumptions that required further justification. Any errors or suggestions identified during the quality check were addressed prior to submission.

3.12.2 External validation of cost-effectiveness analysis

External validation of model inputs and assumptions was undertaken through engagement with UK clinical experts. Four consultant dermatologists were initially consulted, all of whom regularly manage adult patients with HH referred from primary care. These specialists worked in either secondary care or community-based dermatology clinics and had recent experience (within the past year) using or recommending at least two of the following treatments: botulinum toxin, iontophoresis, topical GPB, or oral anticholinergics.

Feedback was collected via one-to-one interviews. An additional follow-up interview was conducted with one of the initial four dermatologists to further clarify and validate specific assumptions. The insights gained from these consultations informed the model structure and helped ensure that its inputs and assumptions accurately reflect real-world clinical practice in the UK. All feedback is documented in a detailed data on file and is cited throughout this submission alongside relevant assumptions.

External validation of the model results was also conducted by comparing outcomes with those reported in previously published economic evaluations identified through the SLR presented in Appendix E. Four relevant models were identified, two of which (Bloudek et al. (2021) and Wade et al. (2017)) reported QALY estimates that allow for comparison with those generated by the model submitted in this submission.

Bloudek et al. (2021) reported QALY estimates of 3.75 for glycopyrronium tosylate and 3.63 for topical aluminium chloride across a 5-year time horizon. When the submitted model is run over a comparable 5 year time horizon, it produces similar QALY estimates: 3.69 for GPB 1% cream and 3.60 for antimuscarinics, supporting the external validity of the results.

Wade et al. (2017), which used a lifetime horizon, reported a range of QALYs (18.47 to 19.85) across various treatment sequences. These are generally aligned with the lifetime QALY estimates in the submitted model (17.28 to 17.40). However, direct comparison is limited as Wade et al. (2017) included sequences and treatments not relevant to current UK clinical practice (e.g., iontophoresis, curettage, endoscopic thoracic sympathectomy). Wade et al. (2017) was also the only study to report costs in GBP from a UK healthcare perspective, but these are not directly comparable due to the inclusion of non-applicable treatments.

3.13 Interpretation and conclusions of economic evidence

An economic model has been developed for GPB 1% cream based on existing literature, the treatment pathway for severe PAHH in the UK, and UK clinical feedback. The model is aligned with outcomes which matter to patients i.e., the HDSS score.

The analysis demonstrates that GPB 1% cream is dominant compared to both antimuscarinics and botulinum toxin, delivering greater health benefits at lower overall costs. Compared to antimuscarinics, GPB 1% cream provides an additional +0.16 QALYs with cost savings of £390. Compared to botulinum toxin, GPB 1% cream provides an additional +0.16 QALYs with cost savings of £1,635. These benefits are primarily driven by longer treatment duration with GPB 1% cream, sustained HDSS response, and lower AEs. While the

extended treatment duration with GPB 1% cream leads to higher acquisition costs compared to both antimuscarinics and botulinum toxin, these are offset by lower adverse event costs, reduced need for subsequent therapies, and, in the case of botulinum toxin, lower administration costs.

The results remain robust across all sensitivity analyses, with probabilistic findings closely aligning with the deterministic outcomes. GPB 1% cream is consistently cost-effective, showing a positive NMB at a WTP threshold of £20,000 in all but one sensitivity analysis - the exception being based on wide confidence intervals for HDSS health state utility values from the literature, which are considered clinically implausible when varied in isolation. Across all scenario analyses, GPB 1% cream continues to demonstrate cost-effectiveness with a positive NMB at the £20,000 threshold.

Additionally, GPB 1% cream offers key societal benefits which are not reflected in the economic model. Its topical application, safety profile, and ability to be prescribed and monitored in primary care improve patient convenience and thus HRQoL, which is not fully captured within the economic model. Primary care prescribing increases accessibility, reduces travel time, and minimizes disruption to daily life, particularly for working-age individuals. Compared to oral antimuscarinics, GPB 1% cream is safer, easier to manage, and preferred by patients who dislike oral medications. It also reduces the need for hospital visits, unlike antimuscarinics and botulinum toxin, which require secondary care.

Despite the challenges in collecting robust data on severe PAHH, which has resulted in limited comparator data, the model demonstrates that GPB 1% cream represents a cost-effective use of NHS resources across all scenarios and is cost saving under the base case assumptions.

Overall, a positive NICE recommendation for GPB 1% cream would provide patients and clinicians with a new treatment option which would improve access to effective symptom management, reduce the burden of travel and clinic visits, enhance quality of life, offer a safer, more convenient alternative to existing treatments, and reduce healthcare costs through decreased reliance on secondary care, making it a cost-effective solution for both patients and the healthcare system.

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Appendices

Appendix A Summary of Product Characteristics and UK Public Assessment Report

Appendix B Identification, selection and synthesis of clinical evidence

Appendix C Subgroup analyses

Appendix D Adverse reactions

Appendix E Published cost-effectiveness studies

Appendix F Health-related quality of life studies

Appendix G Cost and healthcare resource identification, measurement and valuation

Appendix H Clinical outcomes and disaggregated results from the model

Appendix I Price details of treatment included in the submission

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Glycopyrronium bromide cream (Axhidrox®) for treating severe primary axillary hyperhidrosis [ID6487]

Summary of Information for Patients (SIP)

May 2025

File name	Version	Contains confidential information	Date
ID6487_Glycopyrronium-bromide-PAHH_SIP_v1.0_[noCON]	1.0	No	20 May 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Glycopyrronium bromide (GPB) 1% cream [brand name - Axhidrox®]

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

GPB 1% cream is for adults with severe primary axillary hyperhidrosis i.e., severe excess sweating at the underarms.[1] These are patients for whom lifestyle changes and/or topical aluminium antiperspirants have been insufficient in managing their excess sweating.[2] GPB 1% cream is an alternative option to oral anticholinergic tablets such as propantheline bromide and oxybutynin, the long-term use of which is frequently hampered by intolerable adverse effects, the most common being dry mouth.[3] GPB 1% cream is also an alternative to botulinum toxin A (Botox) injections which are offered in secondary care in some areas of the country.[4]

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

GPB 1% cream is licensed for the topical treatment of severe primary axillary hyperhidrosis in adults in 23 Member States of the European Economic area.[5] Approval for the UK from the MHRA is expected in the first half of 2025.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Nothing to declare

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Sweating is an important way to reduce the body's temperature, for example during strenuous physical activity or when exposed to a hot environment.[6] Hyperhidrosis is a common skin condition where sweating occurs more than is necessary to maintain normal body temperature.[6] Where hyperhidrosis occurs without a known cause it is referred to as primary hyperhidrosis.[6] Primary hyperhidrosis mainly affects focal areas of the body, such as the armpits, feet, hands or head and face.[6]

Primary hyperhidrosis usually starts before the age of 18 years, although it can happen at any age, and is usually life long.[6] The true prevalence of hyperhidrosis is unknown, as it is often under-reported by patients and under-diagnosed by healthcare professionals.[6] Hyperhidrosis is estimated to occur in 1% to 1.6% of people in the United Kingdom.[7] It affects both sexes and all races equally. Around 90% of these are primary hyperhidrosis and more than half affect the axilla (armpits).[8]

It is estimated that approximately 720,000 adults in England and Wales are living with hyperhidrosis. [7,9] Of these approximately 170,000 are estimated to have severe primary axillary hyperhidrosis.[7,9]

The severity of hyperhidrosis can be assessed using the Hyperhidrosis Disease Severity Scale (HDSS).[10] This tool is commonly used in clinical trials, and can be used in clinical practice, although this is less common.[11]

Figure 1 Summary of the Hyperhidrosis Disease Severity Scale scoring[10]

Hyperhidrosis Disease Severity Scale	
"How would you rate the severity of your hyperhidrosis?"	
☐ 1.	My sweating is never noticeable and never interferes with my daily activities
☐ 2.	My sweating is tolerable but sometimes interferes with my daily activities
☐ 3.	My sweating is barely tolerable and frequently interferes with my daily activities
☐ 4.	My sweating is intolerable and always interferes with my daily activities

A score of 3 or 4 indicates severe hyperhidrosis, and a score of 1 or 2 indicates mild or moderate hyperhidrosis.[10] Patients with primary hyperhidrosis and severe sweating of the armpits would be referred to as having severe primary axillary hyperhidrosis.[10]

Hyperhidrosis can have a significant negative impact on patient quality of life both socially and in the workplace and has been shown to have a greater impact on quality of life than other skin conditions such as atopic eczema, acne, psoriasis, or rosacea.[12] Patients with hyperhidrosis report a high level of psychological strain with an increased association of hyperhidrosis with anxiety and depression.[12] Excessive sweating affects activities of daily living such as wearing clothes, hygiene, and running errands.[12] Excessive sweating can result in embarrassment, anxiousness, sadness, anger, and feelings of hopelessness.[12] Patients with hyperhidrosis may have difficulty in most aspects of social relationships such as physical contact, personal relationships, and intimacy.[12] Patients report distress from a lack of being able to hide their symptoms and low self-esteem from worrying about other peoples' perceptions of them.[13]

> *"I have had hyperhidrosis for about 10 years, since I was a teenager. I get hot flushes and then my face, neck, hair and upper body area will be soaked in perspiration, and I have to change my top literally ten times a day! To be honest if I have to suffer with this condition for the rest of my life, it wouldn't be worth living, that's how severe it is. I wish other people understood how bad hyperhidrosis can be and how badly it can affect the whole of your life."* Quote taken from anonymised patient testimonies from the James Lind Hyperhidrosis Priority Setting Partnership 2017–2019.[14]

Many people with hyperhidrosis are embarrassed to seek medical help, and only half ever discuss their condition with a healthcare professional (HCP).[15] People with hyperhidrosis can spend significant time and money attempting to self-manage their condition with over-the-counter treatments, and specialist clothing such as absorbent underarm pads.[9] The first line of treatment is strong antiperspirants containing aluminium chloride or aluminium chloride hexahydrate.[2] These are often not effective for patients with severe hyperhidrosis and can cause skin irritation.[2] Oral anticholinergic tablets can be used however only one, propantheline bromide, has a license the treatment of hyperhidrosis, and rates of discontinuation over 30% are reported due to adverse events, the most frequent being dry mouth.[16] Botulinum toxin a, commonly known as Botox, is approved for the treatment of primary axillary hyperhidrosis,[17] and repeat injections are required approximately every 6 months.[3] Treatment on the NHS requires referral to secondary care and access to treatment is limited: treatment is not available in all areas of England and Wales, and where treatment is available there may be restrictions on the number of injections per year, or the total number of injections provided by the NHS.[18–20]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

The NHS website advises patients to see a general practitioner (GP) if you're sweating excessively and:[4]

- things you can do yourself are not helping
- it's lasted for at least 6 months
- it stops you from getting on with your daily activities
- it happens at least once a week
- it happens at night (you're having night sweats)

- you have a family history of excessive sweating
- you're taking medicine for another condition

Before presenting to an HCP, patients have often tried various lifestyle adjustments such as wearing loose fitting clothing and wearing white or black coloured clothing to minimise the appearance of excess sweat.[18] Where these initial interventions aren't enough to manage, patients may try non-prescription options such as stronger antiperspirants available over the counter and armpit or sweat shields worn under clothing to absorb excess sweat and protect clothing.[4,18]

When a patient does have an appointment with a GP, hyperhidrosis is usually diagnosed based on a patient's symptoms.[2] GP will assess for any secondary causes of hyperhidrosis such as drugs and disease-driven hormonal abnormalities.[2] A GP may refer a patient for screening blood tests if they think another condition may be causing the excess sweating.[2] Primary hyperhidrosis can be diagnosed where there is visible sweating, which interferes with daily activities, has lasted at least six months, and for which there is no known cause.[2] Severity may be assessed with the assistance of a tool like HDSS and/or through discussion with the patient about their history and the impact hyperhidrosis is having on their quality of life.[2]

No new diagnostic tests are required for treatment with GPB 1% cream.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Initial treatment for primary axillary hyperhidrosis is a one-month trial of topical 20% aluminium chloride antiperspirant applied daily to dry skin.[2] Unfortunately, skin irritation is very common and often forces discontinuation of the treatment.[2,3] In addition, while there is some evidence for the effectiveness of 20% aluminium for mild and moderate primary axillary hyperhidrosis, there is no evidence for effectiveness for severe primary axillary hyperhidrosis.[3]

Where topical aluminium chloride antiperspirant fails to provide satisfactory results for a patient's primary axillary hyperhidrosis, in some areas GPs will trial an oral anticholinergic,[11] or patients are referred to secondary care to access oral anticholinergics and botulinum toxin a (Botox).[2,3]
Figure 2 illustrates the current treatment pathway for primary axillary hyperhidrosis.

While oral anticholinergics can be effective for primary axillary hyperhidrosis, for greatest effect they need to be taken daily and in practice their use is often limited by the side effects that frequently occur, the most common being dry mouth and constipation.[3,11,16]. Because of the side

effects, patients are often advised to use oral medications only when most necessary (e.g. when going to public events), rather than daily.[3] Access to oral anticholinergics is variable across the country.[11] Propantheline bromide is the only option licensed for the treatment of hyperhidrosis,[21] so in some areas this is the only option that GPs will prescribe.[11] In some areas the decision to start a patient on oral anticholinergics is considered a decision for specialists, so patients need to be referred to secondary care or GPs need to receive advice from a dermatologist before initiating treatment.[11]

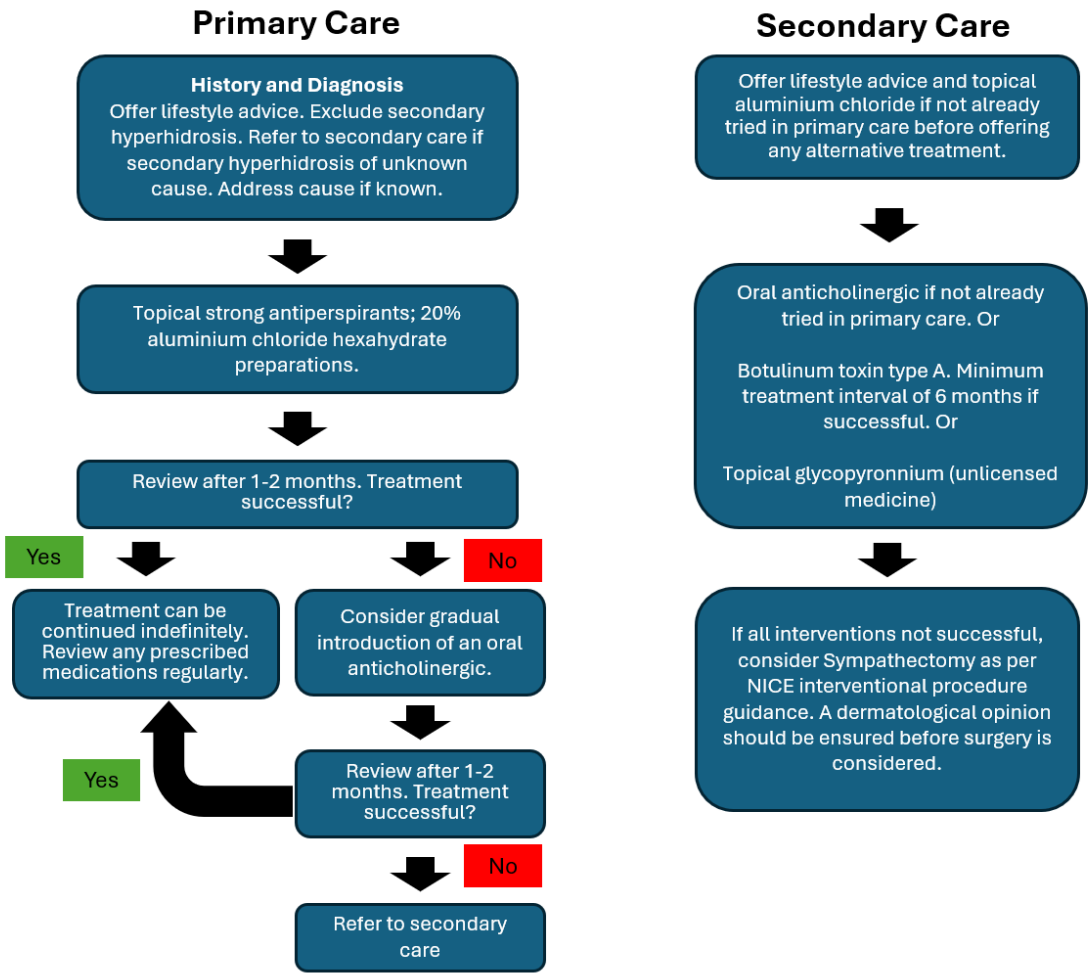
Botox injections can be effective for primary axillary hyperhidrosis and Botox has a license for use in primary axillary hyperhidrosis after initial treatment has proved ineffective.[17] For patients where Botox is effective, repeat injections approximately every 6 months are required to maintain effectiveness.[3] Access to Botox through the NHS is not available in all areas of England and Wales.[11,18,19,20] Where Botox is available there can be restrictions on the number of treatments available per year or the total number of treatments that will be provided by the NHS.[18–20] As a result, patients wanting access to Botox often have to pay for treatment from a private provider.[11]

For patients for whom oral anticholinergics and Botox have failed to provide sufficient control of their hyperhidrosis, in a few centres, an unlicensed preparation of topical GPB is used, as this is recommended by the British Association of Dermatology as an unlicensed medicine to use for severe sweating of the head. Some centres will also try this for patients with severe armpit sweating.[11]

The last option is surgery.[2,3] Localised resection of eccrine sweat glands can be carried out using local anaesthesia, and is useful for small areas of axillary hyperhidrosis. Endoscopic thoracic sympathectomy (ETS) may be offered if other measures are ineffective or not tolerated. This surgery aims to prevent the transmission of nerve signals to the areas producing excessive sweating. This is rarely performed in the UK because of the risk of excess sweating in a different body site that can be worse than the original sweating.[2,3]

GPB 1% cream is anticipated to be used in primary care after an unsuccessful trial of aluminium chloride antiperspirants or to be offered in secondary care before consideration of other treatments if it had not been trialled in primary care.

Figure 2 Schematic to illustrate current treatment pathway for primary axillary hyperhidrosis[1–3]



2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

The James Lind Alliance (JLA) is a non-profit making initiative, established in 2004. It brings patients, carers and clinicians together in Priority Setting Partnerships (PSPs). These partnerships identify and prioritise uncertainties, or 'unanswered questions', about the effects of treatments that they agree are the most important.[15] In July 2017 a Hyperhidrosis PSP was established to identify the unanswered questions about hyperhidrosis treatment and management from patient and clinical perspectives and then prioritise those that patients and clinicians agree are the most important.[15] The top 10 research priorities for treatment and management of hyperhidrosis identified in the PSP were:[15]

Rank Research priority

1. Are there any safe and effective permanent solutions for hyperhidrosis?
2. What is the most effective and safe oral treatment (drugs taken by mouth) for hyperhidrosis?
3. What are the most effective and safe ways to reduce sweating in particular areas of the body (e.g. hands, feet, underarms, face, head)?
4. How does hyperhidrosis affect quality of life?
5. Are combinations of different treatments more effective than one type of treatment for hyperhidrosis?
6. What is the most safe and effective treatment for mild to moderate hyperhidrosis?
7. Could targeted therapies or biologics (e.g. antibodies, hormones, stem cells), be effective in treating hyperhidrosis?
8. What is the most effective severity scale that can be used to determine if a person is eligible for hyperhidrosis treatment?
9. What is the safest and most effective surgery for hyperhidrosis?
10. How safe are hyperhidrosis treatments at different stages of life, e.g. childhood, pregnancy and breastfeeding?

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Eccrine sweat glands are the most common type of sweat glands, found throughout the body and opening directly onto the skin's surface.[22] They play a crucial role in thermoregulation by secreting sweat to cool the skin through evaporation.[22] Eccrine sweat glands have most of their nerves supplied by the sympathetic nervous system via cholinergic pathways.[22] The sympathetic nervous system is part of the autonomic nervous system and is primarily responsible for the "fight or flight" response, preparing the body for stressful situations.[22] Acetylcholine acts as a neurotransmitter in the sympathetic nervous system and is released by the postganglionic neurons to stimulate sweat secretion.[22]

GPB is an anticholinergic. Anticholinergics are medications that block the action of acetylcholine. Anticholinergics inhibits acetylcholine-driven effects on smooth muscle and on various glands,

including the sweat glands. This inhibition of acetylcholine reduces the activity of the sweat glands leading to a decrease in sweating.[23]

Oral anticholinergics have been used in the treatment of hyperhidrosis for several years.[2,3] Oral use is associated with improvements in QoL and clinical symptoms but at the cost of considerable systemic adverse events.[24,25] Topical administration of GPB at the armpit offers a more localised approach to treating hyperhidrosis with a low potential for systemic side effects.

Prior to GPB 1% cream, there had not been a licensed topical anticholinergic treatment for severe primary axillary hyperhidrosis in Europe. Patients in the USA and Japan have been able to access topical anticholinergics for several years,[26,27] but it has been an area of unmet need for patients in the UK. Unlike the topical anticholinergics available in other parts of the world that require daily application, GPB 1% cream allows for a reduced dosing frequency (in the clinical study, by the end of 72 weeks, patients were using GPB 1% cream on average 3 times a week),[28] which is expected to be beneficial to patients for long-term treatment.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

No, GPB 1% cream does not need to be administered in combination with any other medicines.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

The recommended dosage of GPB 1% cream is two pump actuations per armpit (equivalent to 540 mg of cream or 4.4 mg glycopyrronium per armpit).[1] After priming, the pump must be pressed down all the way twice to get the desired dose of 540 mg cream (4.4 mg glycopyrronium).[1]

During the first 4 weeks of treatment, GPB 1% cream is applied to each armpit evenly, once a day, preferably in the evening.[1] From the 5th week on, the frequency of application of GPB 1% cream may be reduced to twice a week, depending on the reduction of axillary sweating.[1] Continuous treatment of primary axillary hyperhidrosis with GPB 1% cream is required to maintain the effect.[1]

The cap can be used for application to help avoid accidental administration of GPB 1% cream to the face/eyes through inadvertent transfer from the hands.[1]

Figure 3 Summary of preparation and application of GPB 1% cream[1]

Preparation of the pump before the first use

The multidose container requires priming before it is used for the first time.
To get a full initial dose, the air trapped in the pump must be removed as follows:

- Hold the pump at an angle (see illustration) and repeatedly press the pump down until cream comes out of the opening onto a piece of paper.
- Slowly push the pump down fully another 10 times and put the pumped cream onto the paper. Dispose the paper with the dispensed cream via waste bin only.
- The pump is now ready for use. Repeated preparation of the pump is not necessary for subsequent use.

Regular application of the cream

After priming, the application of the cream is done using the cap as further detailed:

- Hold the pump in one hand with the opening of the pump towards the removed cap of the pump (see illustration).
- Fully press the pump twice to apply the recommended amount of cream to the top of the cap.
- Using the cap, evenly distribute the cream in one armpit.
- Repeat this process for the second armpit.
- Afterwards, for safety, wash the cap and your hands immediately and thoroughly with soap and water. This is important to avoid contact of the cream with nose, eyes or mouth as well as with other persons
- Tick off the number of treatments in the table on the outer carton

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

GPB 1% cream was studied in a multi-centre, randomised, double-blind and placebo-controlled Phase 3 study that consisted of two phases.[28,29] The first part of the study, Phase 3a, evaluated efficacy and safety of GPB 1% cream compared with placebo for 4 weeks.[29] The second part, Phase 3b, was a long-term efficacy and safety study of GPB 1% cream for 72 weeks.[28]

In Phase 3a, patients self-administered GPB 1% cream or placebo cream, to both armpits once daily preferably in the evening for 4 weeks.[29] In Phase 3b, newly enrolled patients (including placebo patients from Phase 3a) self-administered GPB 1% cream to both armpits once daily for 4 weeks.[28] After 4 weeks initial daily dose administration, all patients, administered the GPB 1% cream as-needed (at least twice per week and not more than once daily) until Week 72.[28,29] Both studies are summarised in the table below.

Trial[28,29]	Combined Randomised, Double-blind, Dose-confirming Phase 3a Study in Parallel Design to Assess the Efficacy and Safety of Topical 4-week Treatment With 1% GPB Cream vs Placebo and Open-label Phase 3b Study to Assess Long-term Efficacy and Safety in Patients With Primary Axillary Hyperhidrosis Treated With GPB 1% Cream **Phase III:** Completed **Location(s):** Germany, Poland, Hungary, UK, Denmark, and Sweden **Study completion date:** February 2022

Trial design	Randomised, parallel assignment, quadruple masking (participant, care provider, investigator, outcomes assessor)
Population	N=518; aged 18 years to 65 years; body mass index of 18-32 kg/m^2; diagnosis of severe primary axillary hyperhidrosis with a HDSS score of 3 or 4. Resting axillary sweat production in each axilla of > 50 mg in 5 min
Selected exclusion criteria	Hypersensitivity to GPB, secondary hyperhidrosis, previous surgical treatment for hyperhidrosis, Botox treatment in the 4 months prior to the study
Intervention	GPB 1% cream
Comparators	Phase 3a Placebo (vehicle cream). Phase 3b none
Primary Outcomes	**Phase 3a:** Absolute change in sweat production assessed by gravimetric measurement [Baseline to day 29] **Phase 3b:** (only for newly recruited patients): Absolute change in sweat production assessed by gravimetric measurement [Baseline to week 12]
Key Secondary Outcomes	**Phase 3a:** Comparison between GPB 1% cream and placebo regarding absolute change in HidroQoL score from baseline to day 29 and the percentage of responders based on HDSS score at day 29 (improvement of ≥ 2 points) **Phase 3b:** Percentage of responders with a ≥2-point improvement from baseline at weeks 12 and 28, as assessed by HDSS, and the absolute change in HidroQoL score from baseline to week 12. Absolute change in the HDSS, HidroQoL and DLQI from baseline to weeks 4, 8, 12, 28, 52 and 72

As hyperhidrosis often starts in adolescence, a follow-up study of GPB 1% cream in patients aged 12–17 years has been conducted to evaluate the safety and efficacy in patients within this age group. This trial is summarised below.

Trial	An Open-label, Uncontrolled, Multicentre Study to Evaluate the Safety, Local Tolerability, Systemic Exposure, and Efficacy of GPB 1% Cream in Adolescents With Severe Primary Axillary Hyperhidrosis **Phase II:** Completed **Location(s):** Germany **Study completion date:** June 2024
Trial design	Open-label, Uncontrolled, Multicentre Study
Population	N=42; aged 12 years to 17 years; body mass index percentile ≥10 and ≤90; diagnosis of severe primary axillary hyperhidrosis with patient-rated hyperhidrosis severity (PRHS) score of ≥5 with symptoms for at least 3 months before Screening. Resting axillary sweat production in each axilla of > 50 mg in 5 min
Selected exclusion criteria	Hypersensitivity to GPB, secondary hyperhidrosis, previous surgical treatment for hyperhidrosis, Botox treatment in the 4 months prior to the study
Intervention	GPB 1% cream
Comparators	None
Outcomes	**Primary outcomes** Number of patients with Adverse Drug Reaction during treatment [Baseline to Day 57]

	Number of patients with a local tolerability assessment (skin reaction score) >0 during treatment [Baseline to Day 57] Absolute change in GP plasma concentration [Baseline to Day 15] **Secondary outcomes** Change in sweat production Proportion of responders Quality of Life
Publications	Awaiting publication. Abstract N°: 6264, European Academy of Dermatology and Venereology (EADV) Congress 2024, Amsterdam 25 SEPTEMBER - 28 SEPTEMBER 2024 https://eadv.org/wp-content/uploads/scientific-abstracts/EADV-congress-2024/Miscellaneous.pdf

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Together with improvement in quality of life, absolute sweat reduction is a key treatment goal for severe primary axillary hyperhidrosis.[3] This can be measured objectively by comparing volume of sweat production (gravimetric sweat) before treatment and at different time points during treatment.[30] It can also be measured subjectively, by measuring HDSS scores before treatment and at different time points during treatment.[10] A 1-point improvement in HDSS score has been associated with a 50% reduction in sweat production and a 2-point improvement with an 80% reduction.[10]

Gravimetric sweat

How this was measured[28,29]
Gravimetric measurements were conducted at room temperature and at a humidity consistent with the normal local climate. After a period of at least 30 min to get used to the room temperature, armpit hair was trimmed, and armpits were dried with an absorbent paper towel. Standardized filter paper was placed on both armpits for 5 min. Weighing of the standardized filter paper before and after the gravimetric measurements was performed in a central laboratory.

Outcomes Phase 3a[29]
After 4 weeks of treatment the group treated with GPB 1% cream showed a larger, approximately 2-fold, sweat reduction from baseline than the placebo group. Mean sweat production was reduced by 197.08 mg for the GPB 1% cream group and 83.49 mg for the placebo group. Absolute reduction in sweat production from baseline to day 29 was statistically significantly larger (p=0.004) in the GPB 1% cream group than in the placebo group. In the placebo-controlled Phase 3a study, overall, the proportion of patients achieving a certain degree of sweat reduction was approximately twofold higher for the GPB 1% cream than for placebo (1.7-fold for a 50% reduction and 2.4-fold for a 90% reduction).

Outcomes Phase 3b[28]

Sweat production was significantly reduced compared to baseline, 4 and 12 weeks after treatment with GPB 1% cream (p <0.0001). Median total sweat production was 212.4 mg at baseline and 75.8 mg after 12 weeks of treatment with GPB 1% cream. Absolute change was statistically significant. The proportion of responders who achieved a reduction in sweat production ≥50% was 54.1% at week 12. Approximately every third patient achieved a reduction of ≥75% (36%, p <0.0001) and one in five achieved a reduction of ≥90% at week 12 (22%, p = 0.0005).

Hyperhidrosis Disease Severity Scale

How this was measured[28,29]
As explained above, the HDSS is a disease-specific diagnostic tool for measuring the severity of HH. Each of four possible answers is assigned a value on a 4-point scale ranging from 1 to 4.

Outcomes Phase 3a[29]
Change from baseline that clearly favoured GPB 1% cream treatment over placebo at day 15 (p=0.002) and day 29 (p=0.014). More patients in the GPB 1% group experienced a response to treatment (for day 29). At day 15 there was a significantly higher proportion of patients with an improvement of ≥ 2 points than for placebo (25% (n =22) vs. 9% (n = 8); P = 0.007), while at day 29 the responder rate was similar and the difference between the groups approached statistical significance.

Outcomes Phase 3b[28]
Patients who had a ≥2-point improvement in the HDSS assessment compared to baseline values were defined as responders to treatment. The pre-specified key secondary end point stated that the percentage of responders with a ≥2-point improvement should be greater than 25%. The proportion of responders was statistically significant at week 28 (29%, p=0.0112) and onwards (30%, p=0.0072 and 32%, p=0.0002 for week 52 and week 72, respectively).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Patient reported outcomes were included in the clinical studies for GPB 1% cream to determine the impact of treatment on patient quality of life. Hyperhidrosis and dermatology specific QoL tools were used rather than a generic tool like EQ-5D, which is a standardised measure of health-related quality of life that provides a simple, generic questionnaire for use in clinical and economic appraisal and population health surveys and is commonly used across clinical studies for different conditions.[31] Using hyperhidrosis specific measures such as HidroQoL was deemed appropriate for the clinical trials, and previous work had shown that the domains used in EQ-5D don't fully reflect the burden of HH.[32]

Patient representatives had previously reported that that the HidroQoL tool was superior to the other tools commonly used in hyperhidrosis research for assessing quality of life.[3] They

commented that it covers everything important to patients with hyperhidrosis and is easy to complete.[3] They considered that measuring the actual amount of sweat produced (e.g. by gravimetry) was less important than measuring quality of life.

Hyperhidrosis Quality of Life Index (HidroQol)

Description[28,29]
The HidroQoL is a validated patient-reported outcome measure used to capture the QoL of patients with HH. Two domains are assessed; daily life activity and psychosocial life (psychological and social factors that influence an individual's well-being and functioning)

Phase 3a results[29]
Median improvement in HidroQoL total score was significantly greater for was significantly greater for GPB 1% cream (–6.0 points) than for placebo (–1.0 point; P < 0.001) on day 29. Similar results were observed for the individual domains of daily life activity and psychosocial life.

Phase 3b results[28]
HidroQoL total score as well as the daily life activities and psychosocial domains improved from baseline to week 12 with statistical significance (median change: −11.0; p <0.0001). Significant decreases in HidroQoL total scores were observed for all study time points (p <0.0001).

Dermatology Life Quality Index (DLQI)

Description[28,29]
DLQI is a validated questionnaire used to measure the impact of skin disease on the QoL of the affected person. It consists of 10 questions that are answered on a 4-point scale from 0 to 3.

Phase 3a results[29]
Median improvement at day 15 was larger for patients in the GPB 1% than for placebo. The improvement seen for the GPB 1% cream was upheld until day 29.

Phase 3b results[28]
Significant decreases in DLQI scores were observed for all study time points (p <0.0001), pointing to a considerable ongoing improvement in the patients' quality of life starting as early as 4 weeks after the first treatment with GPB 1% cream. Changes after week 4 were seen even though the median application frequency was decreased (seven applications per week at week 4 to three applications per week at week 72).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Topical anticholinergic treatment for hyperhidrosis has been developed specifically to achieve local activity at the site of excess sweating and reduce systemic (throughout the body) exposure, thus reducing the rates of anticholinergic adverse events compared to oral anticholinergics.

Available data suggests low systemic absorption of topical GPB 1% cream.[33] The rate of anticholinergic adverse events reported in the studies with GPB 1% cream is considerably lower than the rates reported in studies involving the use of oral anticholinergics for HH,[3,16,28,29] which is expected given the reduced systemic exposure achieved by topical administration.[3,16,28,29]

The safety profile is dominated by adverse events in line with anticholinergic effects, mainly in the facial area such as dry mouth and dry eye, ocular hyperemia (more blood flow to the eye than normal) and of local skin reactions.[28,29] Dry mouth was the most frequent adverse event, reported at an overall frequency of 17.2% for patients treated with GPB 1% cream treated vs 4.8 % for the placebo in the Phase 3a study.[29] Dry mouth rates greater than 35% are reported in the oxybutynin studies included in the NICE evidence summary on oxybutynin for hyperhidrosis.[16] The most common application site reaction was erythema (redness of the skin).[28,29]

In the Phase 3b study, of all adverse events that occurred in more than two patients, dry mouth was the most common in 62 of 518 of patients (12%) even though lower percentage of patients reported dry mouth from week 4 to 72 (5.8%) compared to baseline to week 4 (9.8%).[28]

Topical application of GPB 1% cream was overall well-tolerated with erythema in 37 of 518 patients (7.1%) and pruritus (itchiness) in 18 of 518 patients (3.5%) being the most frequent at the application site adverse event.[28,29] Other adverse events occurred in 3.3% of the patients or less and included dry eye, nasal dryness, visual impairment, and headache.[28,29] All were of mild to moderate severity, and were reversible after applications.[28,29]

GPB 1% cream has a very different adverse event profile to Botox.[3,17,28,29] The most frequently reported adverse events for Botox are injection site pain, and increases in non-axillary sweating, also known as compensatory sweating (increasing in sweating at a body location away from the armpits).[3]

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

1. Significant impact on sweat volume reduction vs placebo. Efficacy similar to oral anticholinergics, but with the ability for greater persistence and long-term results
2. Positive impact on patient QoL in clinical trials. Patients view improvement in QoL to be as important as reduction in sweat volume.
3. Less systemic absorption than oral anticholinergics; improved tolerability and anticipated increased persistence with treatment.
4. Treatment would be available for all patients with severe primary axillary hyperhidrosis, in primary care, unlike Botox.
5. Avoids the injections associated with Botox and the secondary care resource use associated with Botox.
6. Straightforward to use. The patient can flex dose up and down easily based on their response to treatment after the initial four-week period.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

1. GPB 1% cream must be used daily or multiple times a week to maintain effectiveness, however the average application frequency is less than a daily antiperspirant.
2. Some anticholinergic side effects do still occur, however the occurrence is considerably lower than for oral anticholinergics.[2,3,16,28,29]
3. Some local site reactions do occur,[28,29] however there are no injection site reactions like those that can occur with Botox.[3]
4. Care must be taken to ensure no contamination from accidental transfer of GPB 1% cream from hands to eyes; however, the application of the cream using the cap can help to minimise the risk of this.[1]

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Cost-effectiveness assessment of new medicines

To determine whether a medicine provides good value for money to the NHS, NICE uses a measure called the incremental cost-effectiveness ratio (ICER).[34] The ICER compares the new treatment, such as GPB 1% cream, to existing treatments. In this case, these include antimuscarinics (propantheline bromide, off-label oxybutynin, and oral GPB) and botulinum toxin. The ICER calculates the extra cost required to gain one additional quality-adjusted life year (QALY) with the new treatment. A QALY measures both the quantity and quality of life, with one QALY being equivalent to one year of life in perfect health.

The costs included in the ICER calculation are not limited to drug costs, but also include administration costs, monitoring costs, the cost of managing side effects, and the cost of any

subsequent treatments. A treatment is considered cost-effective if it provides additional QALYs at a cost that falls within NICE's acceptable range.

Economic assessment of GPB 1% cream in severe primary axillary hyperhidrosis

The cost-effectiveness of GPB 1% cream was evaluated using a model that compares its benefits and costs to those of antimuscarinics and botulinum toxin over a lifetime horizon. This means the model estimates the expected QALYs and costs over the patient's entire lifetime.
The analysis focused on patients with severe primary axillary hyperhidrosis, which is the population defined in the NICE final scope and aligns with the group studied in the Phase 3a and 3b clinical trials for GPB 1% cream.[28,29,35] It also reflects the expected UK marketing authorisation for GPB 1% cream.

The model considers the treatment costs, as well as the cost of administration, monitoring, management of side effects, and any subsequent treatments. The impact on quality of life was estimated using data from the EQ-5D-3L published in the literature.[32]

Health states in the economic model

The model uses a state transition structure, which tracks how patients move between different health states over time. These health states are defined using the Hyperhidrosis Disease Severity Scale (HDSS), which scores sweating severity from 1 to 4, as well as accounting for subsequent therapies and death. The HDSS is a patient-reported measure that reflects how much daily sweating affects a patient's life.

GPB 1% cream is not expected to impact survival. Instead, its benefits come from improvements in quality of life, which are linked to its effects on HDSS scores, its tolerability, and its convenience as a maintenance therapy - factors that help ensure patients continue using the treatment.

Transitions between health states can happen over time, depending on whether the treatment is effective or whether the patient loses its effect. The state transition model is particularly useful in chronic conditions like primary axillary hyperhidrosis, as it allows for the modelling of patients between distinct health states. In this case the health states are defined by HDSS; this is a patient-reported outcome, thus reflecting outcomes which matter most to patients. Additionally, this model structure uses the short-term clinical study data to predict long-term outcomes. Additionally, the structure aligns with three of the four economic models identified in the literature review.

Each health state is linked to a specific cost and quality of life over a patient's lifetime. Data on how patients are expected to move between these states comes from the Phase 3a and 3b clinical trials for GPB 1% cream, as well as indirect treatment comparisons using literature data for antimuscarinics and botulinum toxin.

Assumptions and limitations

Economic modelling is based on the data available, and several challenges exist in generating high-quality clinical evidence for severe primary axillary hyperhidrosis. These challenges include:

- The subjectivity of symptoms and outcomes.
- The episodic and individualised nature of treatment patterns.
- The stigma and embarrassment that may discourage patients from seeking treatment or participating in studies.
- Healthcare system variability and differences in treatment access.

- The limited investment in research, as severe primary axillary hyperhidrosis is not life-threatening, and treatments are often off-label or relatively low-cost.

Despite these challenges, GPB 1% cream has been evaluated in both a randomised, placebo-controlled Phase 3a trial with a 29-day follow-up, and supported by long-term Phase 3b data, where patients were followed for up to 72 weeks. This reflects one of the longest follow-up periods in primary axillary hyperhidrosis.

However, some uncertainty remains about how GPB 1% cream compares to antimuscarinics and botulinum toxin, as there are no direct head-to-head studies. Indirect comparisons have been used based on the literature for these comparators. For antimuscarinics, there are limited data available for patients with severe primary axillary hyperhidrosis, and the available data comes from a broader hyperhidrosis population over just six weeks. This makes it difficult to interpret the relative effectiveness of GPB 1% cream compared to antimuscarinics. While data on botulinum toxin are available for patients with severe primary axillary hyperhidrosis, these are limited to a four-week period, which doesn't capture the known reduction in efficacy of botulinum toxin over time. There is also some uncertainty about how repeat botulinum toxin treatments impact efficacy. Scenario analyses explore the impact on results from different assumptions underpinning the relative efficacy of GPB 1% cream vs. comparators.

Additionally, the model relies on extrapolating data beyond the 72-week trial period observed for GPB 1% cream in the Phase 3b study. The model assumes that trends observed at the final time points continue across the lifetime horizon for treatment response, loss of response, and treatment discontinuation. These assumptions are explored in scenario analyses.

Finally, GPB 1% cream offers societal benefits not fully captured in the model. Its topical application, safety profile, and ability to be prescribed and monitored in primary care improve patient convenience and health-related quality of life (HRQoL), benefits that are not fully reflected in the economic model.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

The potential for effective treatment of primary axillary hyperhidrosis with topical anticholinergics has long been recognised. While options for patients have been available in other parts of the world for several years, UK patients have not been able to benefit from a licensed treatment option that has been assessed in clinical trials. GPB 1% cream will provide this option for patients. HCPs working in primary care will be able to offer patients an effective and well tolerated treatment option without referral to secondary care.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

No equality issues were identified for this population

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Phase 3 studies of GPB 1% cream

Abels C, Soeberdt M, Kilic A, Reich H, Knie U, Jourdan C, et al. A glycopyrronium bromide 1% cream for topical treatment of primary axillary hyperhidrosis: efficacy and safety results from a phase IIIa randomized controlled trial. British Journal of Dermatology. 2021;185(2):315-22. Available from: https://doi.org/10.1111/bjd.19810.

Szeimies RM, Abels C, Kilic A, Reich H, Berger B, Schulze zur Wiesche E, et al. Long-term efficacy and safety of 1% glycopyrronium bromide cream in patients with severe primary axillary hyperhidrosis: Results from a Phase 3b trial. Journal of the European Academy of Dermatology and Venereology. 2023;37(4):823-30. Available from: https://doi.org/10.1111/jdv.18843.

UK and International Patient organisations

Hyperhidrosis UK https://hyperhidrosisuk.org/
International Hyperhidrosis Society https://www.sweathelp.org/

UK patient information

British Association of Dermatologists Hyperhidrosis patient information leaflet
https://www.bad.org.uk/pils/hyperhidrosis/
British Skin Foundation
https://knowyourskin.britishskinfoundation.org.uk/condition/hyperhidrosis/

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE

4b) Glossary of terms

Clinical trial – a type of research that studies new tests and treatments and evaluates their effects on human health outcomes
Marketing authorisation – Permission to sell a medicine after the evidence (on safety, quality, and efficacy) has been assessed. This is different from NICE's appraisal of a medicine, which also considers whether the medicine is cost-effective for the NHS.

Open-label trial – A trial where people and investigators have knowledge of the assigned treatment.
Randomised trial – A study in which a number of similar people are randomly allocated to receive a specific drug or other intervention (i.e. a group given the medicine being tested) against a control (i.e. group being given a comparator).
Patient reported outcome - a report of a patient's health status directly from the patient, without interpretation by a healthcare professional.
Anticholinergic - drugs that block the action of acetylcholine, a neurotransmitter, in the nervous system.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Glycopyrronium bromide cream (Axhidrox®) for treating severe primary axillary hyperhidrosis [ID6487]

Clarification questions

May 2025

File name	Version	Contains confidential information	Date
ID6487_GPB 1% cream_PAHH_EAG urgent clarification question_v1.0	V1.0	No	30th May 2025

Section A: Clarification on access to individual patient-level data

A1. Priority question: In the submission, the company states that they have a "lack of access to patient-level data from the GPB 1% cream trials". However, the EAG is aware that the company is going through the regulatory process with the MHRA for GPB 1% cream. The EAG considers that it is likely that the company will have required access to the individual patient-level data (IPD) to respond to any MHRA requests. As such, please can the company:

a) Confirm if they do or do not have direct access to the IPD from Hyp-1 Phase 3a and Phase 3b (and explain the apparent discrepancy if they don't have direct access).

b) Confirm if the company has indirect access to the IPD from Hyp-1 Phase 3a and Phase 3b; for example, a route to the IPD data holder where they can request analyses.

Response: Leith Healthcare does not have direct access to the individual patient data (IPD) from the Hyp-1 Phase 3a and Phase 3b clinical trials. The MHRA submission has been made by Dr. Wolff, who hold the IPD. Leith Healthcare does have a route to the IPD data holder where analysis could be requested.

However, it is important to note that the clinical study report (CSR) which is used to inform the submission contains the same data and endpoints that are available for comparators and, in fact, includes more data than what is available for them. Therefore, whilst additional analyses can be requested from Dr Wolff, these data are unlikely to be available for the comparators. As such, these analyses would unlikely add to the evidence on the relative efficacy of GPB 1% cream compared to the comparators. Additionally, the data and endpoints from the CSR which are used within the economic model align with the published assessments of relative efficacy in indirect treatment comparisons presented in Wade et al. (2017), Obed et al. (2021), and El-Samahy et al. (2023).[1–3] Therefore, the data from the CSR are consistent with published assessments of relative efficacy and published economic models.

We remain open to considering suggestions from the EAG that may meaningfully support decision-making. Where appropriate, and subject to timing and prioritisation, we will explore the feasibility of any additional suggested analyses with Dr. Wolff.

References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Glycopyrronium bromide cream (Axhidrox®) for treating severe primary axillary hyperhidrosis [ID6487]

Response to clarification questions

June 2025

File name	Version	Contains confidential information	Date
ID6487_GPB 1% cream_PAHH_Response to EAG clarification questions [CON]	1.0	Yes	26 June 2025

Notes for company

Highlighting in the template

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

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

Section A: Clarification on effectiveness data

Treatment pathway

A1. Priority question. Please clarify the proposed positioning of glycopyronnium bromide (GPB) 1% cream in the treatment pathway as follows:

a) **in primary care, is GPB 1% cream being proposed as an alternative to oral anticholinergics?**
b) **in secondary care, is GPB 1% cream being proposed as a new line of therapy prior to the existing treatment options (oral anticholinergics and botulinum toxin type A) or as an option compared to the existing treatment options?**

Response: GPB 1% cream is proposed as an alternative to oral anticholinergics in primary care. Feedback from experts indicated that some patients currently referred to secondary care have only had treatment with topical aluminium-based antiperspirants. In these situations, GPB 1% cream would be considered as an alternative to oral anticholinergics in secondary care. The significant majority of GPB 1% cream is expected to be initiated in primary care.

A2. Clinical experts consulted by the External Assessment Group (EAG) indicated that glycopyronnium bromide (GPB) 1% cream could be used as an add-on to botulinum toxin type A (BTX) at the point at which the treatment effect starts to wane until the next scheduled treatment (between month 4 and 6).

a) **Please discuss the clinical expert's view and how that aligns with the company's proposed position of GPB 1% cream.**

b) **Please explore what the treatment effectiveness of GPB 1% cream would be as an add-on to BTX during the treatment waning period.**

c) **Please provide a scenario in the economic model for the cost-effectiveness of GPB 1% cream as an add-on to BTX.**

Response (a): No studies have been conducted for GPB 1% cream as an add-on to BTX. Patients were excluded from the clinical trial if they had received BTX within four months. During the phase 3b study patients did not receive BTX (1 patient only for palmar hyperhidrosis). As the first topical anticholinergic antihidrotic licensed in the UK, the place in therapy proposed for GPB 1% cream, as an alternative to oral anticholinergics prior to consideration for BTX, aligns with the clinical trial data and the indication for BTX for severe hyperhidrosis of the axillae which does not respond to topical treatment with antiperspirants or antihidrotics. Clinical experts consulted by the Company have not indicated that 1% GPB cream would only be used in the circumstances mentioned in the clarification question.

Response (b): As outlined in the response to CQ A2a, there is no evidence on the effectiveness of GPB 1% cream in combination with BTX during the waning period, so we cannot determine the potential effectiveness of this combination. However, as also noted in CQ A2a, this is not the expected use of GPB 1% cream in UK clinical practice. Therefore, we do not consider this combination to be a relevant comparator in the economic model.

Response (c): As outlined in the response to CQ A2a and A2b, there is no evidence on the effectiveness of GPB 1% cream in combination with BTX during the waning period, so we cannot determine the potential effectiveness of this combination.

Therefore, including GPB 1% cream in addition to BTX in the BTX treatment arm in the economic model would increase the costs in the BTX arm whilst having an unknown impact on the QALYs. In the original and revised Company base case, GPB 1% cream alone is less costly and more efficacious than BTX alone. Including GPB 1% cream in combination with BTX would increase the incremental costs compared with GPB 1% cream alone, in favour of GPB 1% cream alone. It is unknown what the impact would be on the incremental QALYs. However, as also noted in CQ A2a and A2b, this is not the expected use of GPB 1% cream in UK clinical practice. Therefore, we do not consider this combination to be a relevant comparator in the economic model.

Baseline characteristics

A3. Priority question. Please provide the number of patients in each of the HDSS categories at baseline for the Hyp1-18/2016 Phase 3a study (i.e. the equivalent of Table 22 in the company submission), separately for 1% GPB cream and placebo arms.

Response: Please see the table below for the information requested.

Table 1 HDSS categories at baseline for the Hyp1-18/2016 Phase 3a study

	Placebo, [N; %]	1% GPB Cream; [N; %]
HDSS 2	[redacted]	[redacted]
HDSS 3	[redacted]	[redacted]
HDSS 4	[redacted]	[redacted]

A4. Priority question: It is noted that median values are currently reported in the company submission for many baseline characteristics. Please provide mean values with accompanying standard deviations (and/or 95% Confidence

Intervals) for the following baseline characteristics in the Hyp1-18/2016 Phase 3a trial:

a) **age (years);**

b) **body mass index;**

c) **sweat production (mg);**

d) **body height;**

e) **body weight;**

f) **body surface area; and**

g) **DLQI score.**

Response: The tables below include the means, medians, and standard deviations for the requested baseline characteristics from Hyp1-18/2016 Phase 3a. All information is taken from the relevant CSR.

Table 2 Hyp1-18/2016 Phase 3a baseline values | Age

Treatment	Age [years]								
	N	Missing	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
1% GPB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3 Hyp1-18/2016 Phase 3a baseline values | BMI

Treatment	BMI [kg/m²]								
	N	Missing	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
1% GPB	[redacted]								
Placebo	[redacted]								
Total	[redacted]								

Table 4 Hyp1-18/2016 Phase 3a baseline values | Sweat production

Treatment	Absolute values of total sweat production° [mg]								
	N	Missing	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
1% GBP	[redacted]								
Placebo	[redacted]								

Table 5 Hyp1-18/2016 Phase 3a baseline values | Height

Treatment	Body Height [cm]								
	N	Missing	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
1% GPB	[redacted]								
Placebo	[redacted]								
Total	[redacted]								

Table 6 Hyp1-18/2016 Phase 3a baseline values | Body weight

Treatment	Body Weight [kg]								
	N	Missing	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
1% GPB	[redacted]								
Placebo	[redacted]								

Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7 Hyp1-18/2016 Phase 3a baseline values | BSA

Treatment	BSA [m²]								
	N	Missing	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
1% GPB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 8 Hyp1-18/2016 Phase 3a baseline values | DLQI

Treatment	DLQI								
	N	Missing	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
1% GPB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A5. Priority question: Please provide mean values with accompanying standard deviations (and/or 95% Confidence Intervals) for the following baseline characteristics in the Hyp1-18/2016 Phase 3b trial:

a) **age (years);**

b) **body mass index;**

c) **sweat production (mg);**

d) **body surface area; and**

e) **DLQI score.**

Response: The tables below include the means, medians, and standard deviations for the requested baseline characteristics from Hyp1-18/2016 Phase 3b. All information is taken from the relevant CSR.

Table 9 Hyp1-18/2016 Phase 3b baseline values | Age

Age [years]							
N	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 10 Hyp1-18/2016 Phase 3b baseline values | BMI

BMI [kg/m²]							
N	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 11 Hyp1-18/2016 Phase 3b baseline values | BSA

BSA [m²]							
N	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 12 Hyp1-18/2016 Phase 3b baseline values | Sweat production

Absolute values of total sweat production [mg]							
N	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 13 Hyp1-18/2016 Phase 3b baseline values | DLQI

DLQI							
N	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A6. Priority question. Please provide baseline characteristics (mean and median values with accompanying standard deviations/interquartile ranges and/or 95% Confidence Intervals) for Phase 3b for each of the following subgroups:

a) **1% GPB cream patients from Phase 3a; and**

b) **Placebo patients from Phase 3a.**

Response: These are analyses that have not been previously requested by regulatory or HTA assessment bodies. To provide these data would require the data

holder, Dr Wolff, to re-open the analysis database. The Company is therefore unable to provide these data for the EAG.

A7. The footnote of Table 4 in the company submission states that for sweat production (mg), values below 50 mg at baseline were permitted. This appears to be in contrast to the inclusion criteria described in Section 2.3.2.2 of the company submission. Please explain this discrepancy and comment on whether it may affect the results or their applicability.

Response: Thank you. We appreciate the EAG flagging this. For clarity, we have included the selection criteria and process for its assessment below.

1. The Inclusion criteria was 50 or more mg/5 min sweat per axilla.
2. This inclusion criterion was evaluated at Screening.
3. Weighing was done centrally at a lab in Hamburg, so all samples had to be sent there for evaluation. This took up to 1 week.
4. When the amount of sweat was 50 or higher at Screening, patients were eligible and were allowed to be enrolled
5. At Baseline the amount of sweat was measured again, patient received IMP, the amount of sweat was evaluated in the lab and sent to the site several days later.
6. In case a patient had lower <50 mg/5min at Baseline, this was not as Screen Failure or Drop out, because this inclusion criterion was evaluated at Screening.
7. However, if total sweat production is missing or set to missing at Baseline, the appropriated total sweat production value at Screening will be used as Baseline instead. (SAP chapter 4.8)
8. In addition, this analysis will be performed as a complete case analysis (i.e. only considering patients without missing values at Baseline and Week 12) as well.

Hyp1-18/2016 Phase 3b dosing

A8. Priority question. Please clarify whether patients enrolled in Phase 3b from the placebo arm of Phase 3a received once-daily treatment with GPB 1% cream for the first 4 weeks in Phase 3b similar to the newly recruited patients, and if

not then please explain the expected impact of the difference in treatment regimens (as needed vs once-daily for the first 4 weeks) on the results.

Response: As neither patients nor investigators were aware of their treatment groups, there was no possibility to distinguish between former “Placebo-Patients” or “1% GPB Cream-Patients”. To avoid unblinding during the study, all patients, regardless of their treatment group were allowed to use the cream as-needed after Day 29 (End of Phase 3a Part).

To avoid any biases due to possible differences in the dosing scheme, the primary efficacy endpoint was only evaluated in the FAS newb / PPnewb (only newly recruited patients in the 3b part with the dosing scheme 4 weeks daily and thereafter as needed).

It might have been inaccurate to evaluate the primary efficacy endpoint at week 8, since in theory former “Placebo-Patients” would start treatment with GPB 1% cream only after 4 week. However, based on Phase 1b data, the sponsor was already aware of the fast onset of efficacy regarding the reduction of sweat production (after 2 to 7 applications). Therefore in a worst case scenario, where a former “Placebo-Patient” would apply the 1% GPB Cream only 2x per week, the full effect should be visible after 4 weeks (week 8).

In the opinion of the sponsor this justifies to decision to evaluate further (secondary) efficacy data at week 12 data for all patients (FASb, PPSb)

A9. Priority question. Please provide the mean (and accompanying standard error) number of applications of GPB 1% cream per week in Hyp1-18/2016 Phase 3b during the flexible dosing period of the trial for the following populations:

a) **Full analysis set Phase 3b (FASb);**
b) **1% GPB cream patients from Phase 3a;**
c) **Placebo patients from Phase 3a;**
d) **Phase 3b newly recruited patients.**

Response: The information application frequency is presented in the tables below, all information taken from the CSR. Data for Phase 3b newly recruited patients is not

included as this requires analyses that have not been previously requested and would require reopening the database.

Table 14 Full analysis set Phase 3b (FASb)

Week (calc.)	Number of applications							
	N	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
4	[redacted]							
5	[redacted]							
6	[redacted]							
7	[redacted]							
8	[redacted]							
9	[redacted]							
10	[redacted]							
11	[redacted]							
12	[redacted]							
13	[redacted]							
14	[redacted]							
15	[redacted]							
16	[redacted]							
17	[redacted]							
18	[redacted]							
19	[redacted]							
20	[redacted]							
21	[redacted]							

Week (calc.)	Number of applications							
	N	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
22	[redacted]							
23	[redacted]							
24	[redacted]							
25	[redacted]							
26	[redacted]							
27	[redacted]							
28	[redacted]							
29	[redacted]							
30	[redacted]							
31	[redacted]							
32	[redacted]							
33	[redacted]							
34	[redacted]							
35	[redacted]							
36	[redacted]							
37	[redacted]							
38	[redacted]							
39	[redacted]							
40	[redacted]							

Week (calc.)	Number of applications							
	N	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
41	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
43	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
46	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
47	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
51	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
57	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
59	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Week (calc.)	Number of applications							
	N	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
60	[redacted]							
61	[redacted]							
62	[redacted]							
63	[redacted]							
64	[redacted]							
65	[redacted]							
66	[redacted]							
67	[redacted]							
68	[redacted]							
69	[redacted]							
70	[redacted]							
71	[redacted]							
72	[redacted]							
73	[redacted]							
74	[redacted]							
75	[redacted]							
76	[redacted]							
77	[redacted]							
78	[redacted]							

Table 15 1% GPB cream and placebo patients from Phase 3a. Safety analysis set (Phase 3a) (SAFa)

		Number of applications								
		N	Missing	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
Treatment	Diary week	[redacted]								
1% GPB	[redacted]									
	[redacted]									
	[redacted]									
	[redacted]									
	[redacted]									
	[redacted]									
	[redacted]									
	[redacted]									
	[redacted]									
Placebo	[redacted]									
	[redacted]									
	[redacted]									
	[redacted]									
	[redacted]									
	[redacted]									
	[redacted]									
	[redacted]									
	[redacted]									
	[redacted]									
	[redacted]									

Hyp1-18/2016 Phase 3a and Phase 3b outcomes

A10. Priority question. Please provide mean and 95% confidence intervals for the results for all clinical outcomes for the Hyp1-18/2016 Phase 3a and 3b trials.

Response: The information on sweat production, HDSS, HidroQOL and DLQI is provided below. All information taken from the CSR.

Phase 3a

Table 16 Absolute change in logarithmic sweat production BL to Day 29 between treatments (FASa)

					Back transformation of LSmeans	
Treatment	LSmeans	Standard error	P-value (two-sided alpha=0.05)	95% confidence interval	Ratio of sweat production (Day 29 vs. Baseline)	95% confidence interval
1% GPB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

					Back transformation of LSmeans	
Treatment	Difference in LSmeans	Standard error	P-value (two-sided alpha=0.05)	95% confidence interval	Ratio of sweat reduction (1% GPB vs. Placebo)	95% confidence interval
1% GPB vs. Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 17 Percentage of responders at Day 29 assessed by hyperhidrosis disease severity scale (HDSS) at Day 29 between treatments

Cochran-Mantel-Haenszel test statistic	P-value (two-sided, alpha=0.05)	N	Odds ratio	95% confidence interval of odds ratio
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 18 Absolute change in total HidroQOL score from Baseline to Day 29 (FASa) between treatments stratified by center

Difference in median (1% GPB - Placebo)	N	Number of strata	P-value (two-sided, alpha=0.05)	95% confidence interval
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 19 Absolute change in sweat production assessed by GM from Baseline (Day 1a) to Day 29 (FASa)

Treatment	Mean	t-value	P-value (two-sided alpha=0.05)	95% confidence interval
1% GPB	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]

Table 20 Percentage change in sweat production assessed by GM from Baseline to Day 29 (FASa)

Difference in median (1% GPB - Placebo)	N	Number of strata	P-value (two-sided, alpha=0.05)
[redacted]	[redacted]	[redacted]	[redacted]

Table 21 Percentage of responders assessed by GM on Day 29 (FASa)

Cochran-Mantel-Haenszel test for the proportion of responders of GM (sweat reduction >=50%) between 1% GPB and Placebo at Day 29 stratified by center

Cochran-Mantel-Haenszel test statistic	P-value (two-sided, alpha=0.05)	N	Odds ratio	95% confidence intervall of odds ratio
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cochran-Mantel-Haenszel test for the proportion of responders of GM (sweat reduction >=75%) between 1% GPB and Placebo at Day 29 stratified by center

Cochran-Mantel-Haenszel test statistic	P-value (two-sided, alpha=0.05)	N	Odds ratio	95% confidence intervall of odds ratio
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cochran-Mantel-Haenszel test for the proportion of responders of GM (sweat reduction >=90%) between 1% GPB and Placebo at Day 29 stratified by center

Cochran-Mantel-Haenszel test statistic	P-value (two-sided, alpha=0.05)	N	Odds ratio	95% confidence intervall of odds ratio
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 22 Absolute change in HDSS from Baseline to Day 15 (FASa)

Van Elteren 2-sample test stratified by center

Difference in median (1% GPB - Placebo)	N	Number of strata	P-value (two-sided, alpha=0.05)
[redacted]	[redacted]	[redacted]	[redacted]

Two-sided Wilcoxon signed rank test with 95% Hahn-Meeker confidence intervals

Treatment	Median	P-value (two-sided alpha=0.05)	95% confidence interval
1% GPB	[redacted]	[redacted]	[redacted]

Two-sided Wilcoxon signed rank test with 95% Hahn-Meeker confidence intervals

Treatment	Median	P-value (two-sided alpha=0.05)	95% confidence interval
Placebo	[redacted]	[redacted]	[redacted]

Table 23 Absolute change in HDSS from Baseline to Day 29 (FASa)

Van Elteren 2-sample test stratified by center

Difference in median (1% GPB - Placebo)	N	Number of strata	P-value (two-sided, alpha=0.05)
[redacted]	[redacted]	[redacted]	[redacted]

Two-sided Wilcoxon signed rank test with 95% Hahn-Meeker confidence intervals

Treatment	Median	P-value (two-sided alpha=0.05)	95% confidence interval
1% GPB	[redacted]	[redacted]	[redacted]

Two-sided Wilcoxon signed rank test with 95% Hahn-Meeker confidence intervals

Treatment	Median	P-value (two-sided alpha=0.05)	95% confidence interval
Placebo	[redacted]	[redacted]	[redacted]

Table 24 Percentage of responders assessed by the HDSS on Day 15 (FASa)

Cochran-Mantel-Haenszel test for the proportion of responders of HDSS between 1% GPB and Placebo at Day 15 stratified by center

Cochran-Mantel-Haenszel test statistic	P-value (two-sided, alpha=0.05)	N	Odds ratio	95% confidence interval of odds ratio
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 25 Absolute change in total HidroQOL score from Baseline to Day 15 (FASa)

Van Elteren 2-sample test stratified by center

Difference in median (1% GPB - Placebo)	N	Number of strata	P-value (two-sided, alpha=0.05)
[redacted]	[redacted]	[redacted]	[redacted]

Two-sided Wilcoxon signed rank test with 95% Hahn-Meeker confidence intervals

Treatment	Median	P-value (two-sided alpha=0.05)	95% confidence interval
1% GPB	[redacted]	[redacted]	[redacted]

Two-sided Wilcoxon signed rank test with 95% Hahn-Meeker confidence intervals

Treatment	Median	P-value (two-sided alpha=0.05)	95% confidence interval
Placebo	[redacted]	[redacted]	[redacted]

Table 26 Absolute change in total HidroQOL score from Baseline to Day 29 (FASa)

Van Elteren 2-sample test stratified by center

Difference in median (1% GPB - Placebo)	N	Number of strata	P-value (two-sided, alpha=0.05)
[redacted]	[redacted]	[redacted]	[redacted]

Two-sided Wilcoxon signed rank test with 95% Hahn-Meeker confidence intervals

Treatment	Median	P-value (two-sided alpha=0.05)	95% confidence interval
1% GPB	[redacted]	[redacted]	[redacted]

Two-sided Wilcoxon signed rank test with 95% Hahn-Meeker confidence intervals

Treatment	Median	P-value (two-sided alpha=0.05)	95% confidence interval
Placebo	[redacted]	[redacted]	[redacted]

Table 27 Absolute change in the DLQI Baseline to Day 15 (FASa)

Van Elteren 2-sample test stratified by center

Difference in median (1% GPB - Placebo)	N	Number of strata	P-value (two-sided, alpha=0.05)
[redacted]	[redacted]	[redacted]	[redacted]

Two-sided Wilcoxon signed rank test with 95% Hahn-Meeker confidence intervals

Treatment	Median	P-value (two-sided alpha=0.05)	95% confidence interval
1% GPB	[redacted]	[redacted]	[redacted]

Two-sided Wilcoxon signed rank test with 95% Hahn-Meeker confidence intervals

Treatment	Median	P-value (two-sided alpha=0.05)	95% confidence interval
Placebo	[redacted]	[redacted]	[redacted]

Table 28 Absolute change in the DLQI Baseline to Day 29 (FASa)

Van Elteren 2-sample test stratified by center

Difference in median (1% GPB - Placebo)	N	Number of strata	P-value (two-sided, alpha=0.05)
[redacted]	[redacted]	[redacted]	[redacted]

Two-sided Wilcoxon signed rank test with 95% Hahn-Meeker confidence intervals

Treatment	Median	P-value (two-sided alpha=0.05)	95% confidence interval
1% GPB	[redacted]	[redacted]	[redacted]

Two-sided Wilcoxon signed rank test with 95% Hahn-Meeker confidence intervals

Treatment	Median	P-value (two-sided alpha=0.05)	95% confidence interval
Placebo	[redacted]	[redacted]	[redacted]

Phase 3b

Table 29 Absolute change in logarithmic sweat production BL to week 12 between treatments (FASnewb)

Absolute change from Baseline to Week 12 in total sweat production [mg]							
N	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 30 Percentage of responders assessed by the HDSS (≥2-point improvement from Baseline) at Week 12 (>25%) (FASb)

1-sample binomial test at a significance level of 1.47% (one-sided) for testing the hypothesis that the percentage of responders by HDSS is equal or smaller than 25%

Proportion of responders	P-value (one-sided alpha=0.0147)	Exact one-sided 98.53% Clopper-Pearson confidence interval
[redacted]	[redacted]	[redacted]

Table 31 Percentage of responders assessed by the HDSS (≥2-point improvement from Baseline) at Week 28 (>25%)

1-sample binomial test at a significance level of 1.47% (one-sided) for testing the hypothesis that the percentage of responders by HDSS is equal or smaller than 25%

Proportion of responders	P-value (one-sided alpha=0.0147)	Exact one-sided 98.53% Clopper-Pearson confidence interval
[redacted]	[redacted]	[redacted]

Table 32 Absolute change in the total HidroQoL score from Baseline to Week 12 (FASb)

Two-sided Wilcoxon signed rank test with 97.06% Hahn-Meeker confidence interval

Median	P-value (two-sided alpha=0.0294)	97.06% confidence interval
[redacted]	[redacted]	[redacted]

Table 33 Absolute change in daily life activities domain score from Baseline to Week 12

Absolute change in daily life activities domain score from Baseline to Week 12							
N	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 34 Percentage change in total sweat production assessed by GM from Baseline to Week 4 and Week 12

Percentage change in total sweat production from Baseline to Week 4

Percentage change in total sweat production from Baseline° to Week 4							
N	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Full analysis set – newly recruited (Phase 3b) - N=357

Table 35 Percentage change in total sweat production from Baseline to Week 4

Two-sided Wilcoxon signed rank test with 95% Hahn-Meeker confidence interval

Median	P-value (two-sided alpha=0.05)	95% confidence interval
[redacted]	[redacted]	[redacted]

Table 36 Percentage change in total sweat production from Baseline to Week 12

Percentage change in total sweat production from Baseline° to Week 12*							
N	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Full analysis set – newly recruited (Phase 3b) - N=357

Table 37 Percentage change in total sweat production from Baseline to Week 12

Two-sided Wilcoxon signed rank test with 95% Hahn-Meeker confidence interval

Median	P-value (two-sided alpha=0.05)	95% confidence interval
[redacted]	[redacted]	[redacted]

A11. Priority question. Please provide the results from Hyp1-18/2016 Phase 3b for each of the following subgroups (mean and 95% confidence intervals):

a) **1% GPB cream patients from Phase 3a;**

b) **Placebo patients from Phase 3a;**

c) **Phase 3b newly recruited patients.**

Response: The data for 1% GPB cream patients from Phase 3a and placebo patients from Phase 3a requires analyses that have not been previously performed and would require reopening the database.

Table 38 Phase 3b: Primary endpoint - Absolute change in sweat production from Baseline to Week 12

Total sweat production	FASnewb (N = 357)	PPSnewb (N = 205)
Absolute values [mg], mean (SD)		
Baseline b	[redacted]	[redacted]
Change to Week 12	[redacted]	[redacted]
Logarithmic values, mean (SD)		
Baseline b	[redacted]	[redacted]
Change to Week 12	[redacted]	[redacted]
Mixed effects model for the change from Baseline[c]		
Estimate (97.06% CI)	[redacted]	[redacted]
p-value[d]	[redacted]	[redacted]
Ratio Week 12 vs BL (back transformed estimate and CI)	[redacted]	[redacted]

[a] N = 316. [b] N = 198.

[c] Mean centered logarithmic baseline values as fixed effect and center as random effect.

[d] 2-sided, α = 0.0294.

BL = Baseline, CI = confidence interval, FASnewb = full analysis set (patients newly recruited to Phase 3b), N = number of patients, PPSnewb = per-protocol set (patients newly recruited to Phase 3b), SD = standard deviation, vs = versus.

A12. Priority question. Please provide results from Hyp1-18/2016 Phase 3b for all outcomes at 4 weeks to enable a comparison between Hyp1-18/2016 Phase 3a and Phase 3b. Please provide the 4-week results (mean and median with associated measures of uncertainty) from Hyp1-18/2016 Phase 3b for the following populations:

a) **Full analysis set Phase 3b (FASb);**
b) **1% GPB cream patients from Phase 3a;**
c) **Placebo patients from Phase 3a;**
d) **Phase 3b newly recruited patients.**

Response: For the Phase 3b part these results are only available for the Full analysis set Phase 3b new (FASb new), these results are included below, all information taken from the CSR. The 1% GPB cream patients from Phase 3a and Placebo patients from Phase 3a reflects the Day 29 Data from Phase 3a, these results are included below, all information taken from the CSR.

Table 39 Phase 3a: First key secondary endpoint: Percentage of responders as assessed by the HDSS (≥2-point improvement from Baseline) at Day 29 (FASa, PPSa)

	FASa (N = 171)		PPSa (N = 127)	
HDSS	1% GPB (N = 87)	Placebo (N = 84)	1% GPB (N = 69)	Placebo (N = 58)
Responder rate, N (%)a Difference to placebob	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI) p-valuec	[redacted]	[redacted]	[redacted]	[redacted]

Patients with missing values were considered non-responders.

[a] Percentages are based on the number of patients in each treatment group.

[b] Cochran-Mantel-Haenszel test; FASa: n = 171, PPSa: n = 127. [c] 2-sided, α = 0.05.

CI = confidence interval, FASa = full analysis set (Phase 3a), GPB = glycopyrronium bromide, HDSS = hyperhidrosis disease severity scale, N = number of patients, n = number of patients in the analysis, PPSa = per-protocol set.

Table 40 Phase 3a: Second key secondary endpoint: Change in HidroQoL from Baseline to Day 29 (FASa, PPSa)

	FASa (N = 171)		PPSa (N = 127)	
HidroQoL	1% GPB (N = 87)	Placebo (N = 84)	1% GPB (N = 69)	Placebo (N = 58)
Total score, median (range)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change to Day 29	[redacted]	[redacted]	[redacted]	[redacted]
Median (95% CI)	[redacted]		[redacted]	
p-value[f]	[redacted]		[redacted]	
Daily life activities domain score, median (range)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change to Day 29 Difference to placebo[e]	[redacted]	[redacted]	[redacted]	[redacted]
Median (95% CI)	[redacted]		[redacted]	
p-value[f]	[redacted]		[redacted]	
Psychosocial domain score, median (range				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change to Day 29 Difference to placebo[e]	[redacted]	[redacted]	[redacted]	[redacted]
Median (95% CI) p-value[f]	[redacted]		[redacted]	
p-value[f]	[redacted]		[redacted]	

Data available for: [a] N = 84. [b] N = 81. [c] N = 79. [d] N = 56.

[e] Van Elteren 2-sample test stratified by center with Hodges-Lehmann CI; FASa: n = 163, PPSa: n = 125.

[f] 2-sided, α = 0.05.

CI = confidence interval, FASa = full analysis set (Phase 3a), GPB = glycopyrronium bromide, HidroQoL = hyperhidrosis quality of life index, N = number of patients, n = number of patients in the analysis, PPSa = per-protocol set (Phase 3a).

Table 41 Phase 3a: Absolute change in total sweat production [mg] from Baseline to Day 29 (FASa, N = 171)

Total sweat production	1% GPB (N = 87)	Placebo (N = 84)
Absolute values [mg], mean (SD)		
Baseline	[redacted]	[redacted]
Change to Day 29	[redacted]	[redacted]
Logarithmic values	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]
Change to Day 29 Mean (95% CI)[c]	[redacted]	[redacted]
p-value[d]	[redacted]	[redacted]

[a] N = 77. [b] N = 78.
[c] 1-sample t-test stratified by treatment group. [d] 2-sided, α = 0.05.
CI = confidence interval, FASa = full analysis set (Phase 3a), GPB = glycopyrronium bromide, N = number of patients, SD = standard deviation.

Table 42 Phase 3a: Relative change in sweat production from Baseline to Day 29 (FASa, N = 171)

Relative change sweat production	1% GPB (N = 87)	Placebo (N = 84)
Baseline, median (range) [mg]	[redacted]	[redacted]
Relative change to Day 29 [%][a] Median (95% CI)	[redacted]	[redacted]
p-value[d]	[redacted]	[redacted]
Difference to placebo[e]		
Median	[redacted]	
p-value[d]	[redacted]	

[a] Wilcoxon signed rank test with Hahn-Meeker CIs.
[d] 2-sided, α = 0.05. [b] N = 77. [c] N = 78.
[e] Van Elteren 2-sample test stratified by center; n = 155.
CI = confidence interval, FASa = full analysis set (Phase 3a), GPB = glycopyrronium bromide, N = number of patients, n = number of patients in the analysis.

Table 43 Phase 3a: Responder rate (sweat reduction of ≥50%, ≥75%, and ≥90%) assessed by gravimetric measurement at Day 29 (FASa, N = 171)

Sweat reduction from Baseline	1% GPB (N = 87)	Placebo (N = 84)	Odds ratio (95% CI)[a] (N = 171)	p-value[b]
≥50%	[redacted]	[redacted]	[redacted]	[redacted]
≥75%	[redacted]	[redacted]	[redacted]	[redacted]
≥90%	[redacted]	[redacted]	[redacted]	[redacted]

Patients with missing values were considered non-responders.

[a] Cochran-Mantel-Haenszel test. [b] 2-sided, α=0.05.

CI = confidence interval, FASa = full analysis set (Phase 3a), GPB = glycopyrronium bromide, N = number of patients, n = number of patients in the analysis.

Table 44 Phase 3a: Absolute change in HDSS from Baseline to Day 15 and Day 29 (FASa, N = 171)

	Day 15		Day 29	
HDSS	**1% GPB (N = 87)**	**Placebo (N = 84)**	**1% GPB (N = 87)**	**Placebo (N = 84)**
Baseline, median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline[b]				
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value[g]	[redacted]	[redacted]	[redacted]	[redacted]
Difference to placebo[h] Median	[redacted]		[redacted]	
p-value[g]	[redacted]		[redacted]	

[a] N = 86. [b] Wilcoxon signed rank test with Hahn-Meeker CI.

[c] N = 84. [d] N = 79. [e] N = 83. [f] N = 80.

[g] 2-sided, α = 0.05.

[h] Van Elteren 2-sample test stratified by center; n = 163.

CI = confidence interval, FASa = full analysis set (Phase 3a), GPB = glycopyrronium bromide, HDSS = hyperhidrosis disease severity scale, N = number of patients, n = number of patients in the analysis.

Table 45 Phase 3a: HDSS responder rate at Day 15 (FASa; N = 171)

HDSS	1% GPB (N = 87)	Placebo (N = 84)
Responder rate, N (%)[a]	[redacted]	[redacted]
Difference to placebo[b]		
Odds ratio (95% CI)	[redacted]	
p-value[c]	[redacted]	

Patients with missing values were considered non-responders.

[a] Percentages are based on the number of patients in each treatment group.

[b] Cochran-Mantel-Haenszel test; n = 171. [c] 2-sided, α = 0.05.

CI = confidence interval, FASa = full analysis set (Phase 3a), GPB = glycopyrronium bromide, HDSS = hyperhidrosis disease severity scale, N = number of patients, n = number of patients in the analysis.

Table 46 Phase 3a: Absolute change in HidroQoL questionnaire from Baseline to Day 15 and Day 29 (FASa, N = 171)

	Day 15		Day 29	
HidroQoL	**1% GPB (N = 87)**	**Placebo (N = 84)**	**1% GPB (N = 87)**	**Placebo (N = 84)**
Total score				
Baseline, median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline[b]				
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value[c]	[redacted]	[redacted]	[redacted]	[redacted]
Difference to placebo[d]				
Median	[redacted]	[redacted]	[redacted]	[redacted]
p-value[c]	[redacted]	[redacted]	[redacted]	[redacted]

[a] N = 81.
[b] Wilcoxon signed rank test with Hahn-Meeker CI; Day 15: GPB: N = 85, Placebo: N = 79; Day 29: GPB: N = 84, Placebo: N = 79.
[c] 2-sided, α = 0.05.
[d] Van Elteren 2-sample test stratified by center; Day 15: n = 164, Day 29: n = 163.
CI = confidence interval, FASa = full analysis set (Phase 3a), GPB = glycopyrronium bromide, HidroQoL = hyperhidrosis quality of life index, N = number of patients, n = number of patients in the analysis.

Table 47 Phase 3a: Absolute change in DLQI from Baseline to Day 15 and Day 29 (FASa, N = 171)

	Day 15		Day 29	
DLQI score	**1% GPB (N = 87)**	**Placebo (N = 84)**	**1% GPB (N = 87)**	**Placebo (N = 84)**
Baseline, median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline [b]				
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value[c]	[redacted]	[redacted]	[redacted]	[redacted]
Difference to placebo[d]				
Median	[redacted]	[redacted]	[redacted]	[redacted]
p-value[c]	[redacted]	[redacted]	[redacted]	[redacted]

[a] N = 83.
[b] Wilcoxon signed rank test with Hahn-Meeker CI; Day 15: GPB: N = 85, Placebo: N = 79; Day 29: GPB: N = 84, Placebo: N = 79.
[c] 2-sided, α = 0.05.
[d] Van Elteren 2-sample test stratified by center; Day 15: n = 164, Day 29: n = 163.
CI = confidence interval, DLQI = dermatology life quality index, FASa = full analysis set (Phase 3a), GPB = glycopyrronium bromide, N = number of patients, n = number of patients in the analysis.

Table 48 Phase 3b: Relative change in total sweat production from Baseline to Week 4 and Week 12 (FASnewb)

Table 49 Phase 3b: Absolute change in sweat production from Baseline to Week 4 (FASnewb)

Sweat production	N	Mean (SD)	95% CI	p-value[a] (H_0: median = 0)
Absolute values [mg]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline b	[redacted]	[redacted]	[redacted]	[redacted]
Change to Week 4 Logarithmic values	[redacted]	[redacted]	[redacted]	[redacted]
Baseline b	[redacted]	[redacted]	[redacted]	[redacted]
Change to Week 4	[redacted]	[redacted]	[redacted]	[redacted]

[a] 1-sample t-test, 2-sided, α = 0.05.

CI = confidence interval, FASnewb = full analysis set (patients newly recruited to Phase 3b), N = number of patients, n = number of patients in analysis, SD = standard deviation.

Table 50 Phase 3b: Proportion of responders (sweat reduction of ≥50%, ≥75%, and ≥90%) assessed at Week 4 and Week 12 (FASnewb, N=357)

Table 51 Phase 3b: HDSS responders (improvement of ≥2 points from Baseline) at Weeks 4, 8, 52, and 72 (unequal 25%; FASb)

Visit	N	Number (%)[a] of patients	PR	95% CI[b]	p-value[c] (H_0: PR = 0.25)
Week 4[*]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients with missing values were considered non-responders.

[a] Percentages are based on the number of patients in the analysis set. [b] Clopper-Pearson.

[c] 1-sample binomial t-test; 2-sided, α = 0.05.

[*] Data of newly recruited patients only.

CI = confidence interval, FASb = full analysis set (Phase 3b), H_0 = null hypothesis, HDSS = hyperhidrosis disease severity scale, N = number of patients, PR = proportion of responders.

Table 52 Phase 3b: HDSS responders (improvement of ≥2 points from Baseline) at Week 12 (unequal 50%; FASb, PPSb)

Analysis set	N	Number (%)[a] of patients	PR	95% CI[b]	p-value[c] (H_0: PR = 0.50)
FASb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPSb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients with missing values were considered non-responders.

[a] Percentages are based on the number of patients in the analysis. [b] Clopper-Pearson.

[c] 1-sample binomial t-test; 2-sided, α = 0.05.

CI = confidence interval, FASb = full analysis set (Phase 3b), H_0 = null hypothesis, HDSS = hyperhidrosis disease severity scale, N = number of patients in analysis set, PPSb = per-protocol set (Phase 3b), PR = proportion of responders.

Table 53 Phase 3b: Absolute change in HDSS from Baseline to Weeks 4, 8, 12, 28, 52, and 72 (FASb)

HDSS Visit	N	Median (range)	95% CI[a]	p-value[b] (H_0: median = 0)
Baseline a	[redacted]	[redacted]	[redacted]	[redacted]
Baseline b	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline				
Week 4[c]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]	[redacted]

For roll-over patients, the baseline value was assessed at Baseline a.

[a] Hahn-Meeker. [b] Wilcoxon signed rank test, 2-sided, α = 0.05.

[c] Data of newly recruited patients only.

CI = confidence interval, FASb = full analysis set (Phase 3b), H_0 = null hypothesis, HDSS = hyperhidrosis disease severity scale, N = number of patients, n = number of patients in analysis.

Table 54 Phase 3b: Absolute changes in HidroQoL scores from Baseline to Weeks 4, 8, 28, 52 and 72 (FASb)

[redacted]

[redacted]

Table 55 HidroQoL responders (improvement of ≥4 points from Baseline) at Week 4, 8, 12, 28, 52, and 72 (unequal 25% and unequal 50%) - Phase 3b (FASb)

Visit	n	Number (%)[a] of patients	PR	95% CI[b]	p-value[c] H_0: PR = 0.25	p-value[c] H_0: PR = 0.50
Week 4[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Week 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients with missing values were considered non-responders.

[a] Percentages are based on the number of patients in the analysis. [b] Clopper-Pearson.

[c] 1-sample binomial test, 2-sided, α = 0.05

[d] Data of newly recruited patients only.

CI = confidence interval, FASb = full analysis set (Phase 3b), H_0 = null hypothesis, HidroQoL = hyperhidrosis quality of life index, N = number of patients, n = number of patients in analysis, PR = proportion of responders.

Table 56 Phase 3b: Absolute change in DLQI from Baseline to Weeks 4, 8, 12, 28, 52, and 72 (FASb)

DLQI Visit	N	Median	(range)	95% CI[a]	p-value[b] (H_0: median = 0)
Baseline a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline Week 4[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For roll-over patients, the baseline value was assessed at Baseline a.

[a] Hahn-Meeker. [b] Wilcoxon signed rank test, 2-sided, α = 0.05.

[c] Data of newly recruited patients only.

CI = confidence interval, DLQI = dermatology life quality index, FASb = full analysis set (Phase 3b), H_0 = null hypothesis, N = number of patients, n = number of patients in the analysis.

Table 57 Phase 3b: Absolute change in patient-rated hyperhidrosis severity from Baseline to Weeks 4, 8, 12, 28, 52, and 72 (FASb)

Patient-rated severity Visit	N	Median	(range)	95% CIa	p-valueb (H0: median = 0)
Baseline b	[redacted]	[redacted]	[redacted]	[redacted]	
Change from Baseline					
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The patient-rated hyperhidrosis severity assessment was only implemented in protocol Version 2.0; thus, only a subset of patients had a baseline assessment to calculate the change from Baseline.

[a] Hahn-Meeker. [b] Wilcoxon signed rank test, 2-sided, α = 0.05.

CI = confidence interval, FASb = full analysis set (Phase 3b), H_0 = null hypothesis, N = number of patients, n = number of patients in analysis.

A13. Priority question. Please provide a version of Table 26 (Patients with improvement in HDSS) in the company submission for the following FASb subgroups from Hyp1-18/2016 Phase 3b:

a) **newly enrolled phase 3b patients; and**
b) **phase 3a GPB 1% cream patients and newly enrolled phase 3b patients (i.e. all phase 3b patients excluding those from the placebo arm of phase 3a).**

Response: These are analyses that have not been previously required and would require reopening the database.

A14. Please provide a breakdown by HDSS score (i.e. 1, 2, 3 etc.) for change in HDSS score from baseline for each timepoint in Hyp1-18/2016 Phase 3a and Phase 3b.

Response: These are analyses that have not been previously requested by regulatory or HTA assessment bodies. To provide these data would require the data holder, Dr Wolff, to re-open the analysis database. The Company is therefore unable to provide these data for the EAG.

A15. Priority question. Please provide an analysis to assess the correlation between HDSS and sweat reduction gravimetry change from baseline outcomes for GPB 1% cream in the Hyp1-18/2016 trial using data for absolute reduction.

Response: Correlations between total sweat production and HDSS scores were assessed at baseline (r=[redacted]), week 4 (r=[redacted]), and week 12 (r=[redacted]), with no clear relationship observed. Additionally, correlations between the absolute change in HDSS scores and the absolute change in sweat production from baseline to week 4 and week 12 were also low, with correlation coefficients of r=[redacted] and r=[redacted] at both time points (Figure 1, Figure 2). All analyses were conducted in the FASb population (N=357, newly recruited).

Figure 1: Correlation between absolute change from baseline to week 4 in HDSS score and absolute change from baseline to week 4 in total sweat production (Full analysis set - newly recruited (Phase 3b) - N=357)

Abbreviations: ACB, absolute change from baseline; HDSS, Hyperhidrosis Disease Severity Score

Figure 2: Correlation between absolute change from baseline to week 12 in HDSS score and absolute change from baseline to week 12 in total sweat production (Full analysis set - newly recruited (Phase 3b) - N=357)

Abbreviations: ACB, absolute change from baseline; HDSS, Hyperhidrosis Disease Severity Score

A lack of correlation between HDSS and gravimetric sweat reduction is not unexpected, as the two measures assess different aspects of HH. It is also consistent with findings in the literature.[1] HDSS is a subjective, patient-reported outcome that captures the perceived impact of sweating on daily life, whereas gravimetry provides an objective measurement of sweat volume. Because individuals vary in how much sweating affects them, a small change in sweat volume may lead to a large

improvement in HDSS for some, while others may report little change despite measurable reductions.

Despite the lack of strong correlation between HDSS scores and gravimetric sweat reduction, HDSS remains a relevant and meaningful outcome for evaluating treatment effectiveness in PAHH. As a patient-reported measure, HDSS directly reflects the individual's experience of how sweating affects their daily life, something objective measures cannot fully capture. It is often the perceived burden of sweating, rather than the volume alone, that motivates patients to seek treatment. Furthermore, in real-world practice, treatment success is ultimately determined by whether patients feel their sweating has improved and become manageable. Therefore, improvements in HDSS also align closely with clinical decision-making.

A16. Priority question. Please provide a table with the results for mean, median, percentage sweat reduction, and sweat reduction of ≥50%, ≥75%, and ≥90% from baseline in Hyp1-18/2016 Phase 3a and Phase 3b at week 4, and end of study for Phase 3b along with accompanying 95% confidence intervals and p values. Please provide results for each outcome in each trial as:

a) **absolute reductions; and**
b) **relative reductions.**

Response: Information on number of responders is available and is included below, all information taken from the CSR. Total sweat production was only measured to week 12.

Table 58 Phase 3b: Absolute change in sweat production from Baseline to Week 4 (FASnewb)

Sweat production	N	Mean (SD)	95% CI	p-value[a] (H_0: median = 0)
Absolute values [mg]				
Baseline b	[redacted]	[redacted]	[redacted]	[redacted]
Change to Week 4 Logarithmic values	[redacted]	[redacted]	[redacted]	[redacted]
Baseline b	[redacted]	[redacted]	[redacted]	[redacted]
Change to Week 4	[redacted]	[redacted]	[redacted]	[redacted]

[a] 1-sample t-test, 2-sided, α = 0.05.

CI = confidence interval, FASnewb = full analysis set (patients newly recruited to Phase 3b), N = number of patients, n = number of patients in analysis, SD = standard deviation.

Table 59 Phase 3b: Primary endpoint: Absolute change in total sweat production from Baseline to Week 12 (FASnewb, PPSnewb)

Table 60 Absolute change in logarithmic values of total sweat production from Baseline to Week 12 Full analysis set – newly recruited (Phase 3b)

	Absolute values of total sweat production°* [mg]							
	N	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
Visit								
Screening 2b								
Baseline b								
Week 4								
Week 12								

Table 61 Absolute change from Baseline to Week 12 in total sweat production

Absolute change from Baseline° to Week 12* in total sweat production [mg]							
N	Mean	SD	Min	1st quartile	median	3rd quartile	Max

Table 62 Absolute change from Baseline° to Day 29 in total sweat production. Full analysis set (Phase 3a) (FASa)

Treatment= 1% GPB	Absolute change from Baseline° to Day 29 in total sweat production [mg]								
	N	Missing	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

° Missing baseline values of total sweat production were replaced with valid values from the (repeated) gravimetric measurement at Screening 2a.

Table 63 Phase 3a: Relative change in sweat production from Baseline to Day 29 (FASa, N = 171)

Relative change sweat production	1% GPB (N = 87)	Placebo (N = 84)
Baseline, median (range) [mg]	[redacted]	[redacted]
Relative change to Day 29 [%][a] Median (95% CI)	[redacted]	[redacted]
p-value[d]	[redacted]	[redacted]
Difference to placebo[e] Median [redacted] p-value[d] [redacted]	[redacted]	[redacted]

[a] Wilcoxon signed rank test with Hahn-Meeker CIs.
[d] 2-sided, α = 0.05. [b] N = 77. [c] N = 78.
[e] Van Elteren 2-sample test stratified by center; n = 155.
CI = confidence interval, FASa = full analysis set (Phase 3a), GPB = glycopyrronium bromide, N = number of patients, n = number of patients in the analysis.

Table 64 Full analysis set (Phase 3a) (FASa)

Responder* at Day 29	Treatment				Total	
	1% GPB		Placebo			
	N	%	N	%	N	%
Sweat reduction >= 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sweat reduction >= 75%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sweat reduction >= 90%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 65 Full analysis set (Phase 3a) (FASa)

Cochran-Mantel-Haenszel test for the proportion of responders of GM (sweat reduction >=50%) between 1% GPB and Placebo at Day 29 stratified by center

Cochran-Mantel-Haenszel test statistic	P-value (two-sided, alpha=0.05)	N	Odds ratio	95% confidence interval of odds ratio
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cochran-Mantel-Haenszel test for the proportion of responders of GM (sweat reduction >=75%) between 1% GPB and Placebo at Day 29 stratified by center

Cochran-Mantel-Haenszel test statistic	P-value (two-sided, alpha=0.05)	N	Odds ratio	95% confidence interval of odds ratio
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cochran-Mantel-Haenszel test for the proportion of responders of GM (sweat reduction >=90%) between 1% GPB and Placebo at Day 29 stratified by center

Cochran-Mantel-Haenszel test statistic	P-value (two-sided, alpha=0.05)	N	Odds ratio	95% confidence interval of odds ratio
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 66 Full analysis set – newly recruited (Phase 3b) - N=357 Percentage of responders assessed by GM at Week 4

	N	%
Responder assessed by GM (sweat reduction >= 50%)	[redacted]	[redacted]
no		
yes	[redacted]	[redacted]
Responder assessed by GM (sweat reduction >= 75%)	[redacted]	[redacted]
no		
yes	[redacted]	[redacted]
Responder assessed by GM (sweat reduction >= 90%)	[redacted]	[redacted]
no		
yes	[redacted]	[redacted]
Total	[redacted]	[redacted]

Table 67 Full analysis set – newly recruited (Phase 3b) - N=357 Percentage of responders assessed by GM at Week 12

	N	%
Responder assessed by GM (sweat reduction >= 50%)	[redacted]	[redacted]
no		
yes	[redacted]	[redacted]
Responder assessed by GM (sweat reduction >= 75%)	[redacted]	[redacted]
no		
yes	[redacted]	[redacted]
Responder assessed by GM (sweat reduction >= 90%)	[redacted]	[redacted]
no		
yes	[redacted]	[redacted]
Total	[redacted]	[redacted]

Table 68 Full analysis set – newly recruited (Phase 3b) - N=357

1-sample binomial test at a significance level of 5% (two-sided) for testing the hypothesis that the percentage of responders by GM (sweat reduction >=50%) at Week 4 is equal to 50%

Proportion of responders	P-value (two-sided alpha=0.05)	Exact two-sided 95% Clopper-Pearson confidence interval	Conclusion
[redacted]	[redacted]	[redacted]	The hypothesis that the percentage of responders is equal to [redacted] (proportion of responders equal to [redacted]) was rejected.

1-sample binomial test at a significance level of 5% (two-sided) for testing the hypothesis that the percentage of responders by GM (sweat reduction >=75%) at Week 4 is equal to 25%

Proportion of responders	P-value (two-sided alpha=0.05)	Exact two-sided 95% Clopper-Pearson confidence interval	Conclusion
[redacted]	[redacted]	[redacted]	The hypothesis that the percentage of responders is equal to [redacted] (proportion of responders equal to [redacted]) was rejected.

1-sample binomial test at a significance level of 5% (two-sided) for testing the hypothesis that the percentage of responders by GM (sweat reduction >=90%) at Week 4 is equal to 15%

Proportion of responders	P-value (two-sided alpha=0.05)	Exact two-sided 95% Clopper-Pearson confidence interval	Conclusion
[redacted]	[redacted]	[redacted]	The hypothesis that the percentage of responders is equal to [redacted] (proportion of responders equal to [redacted]) was rejected.

Table 69 Full analysis set – newly recruited (Phase 3b) - N=357

1-sample binomial test at a significance level of 5% (two-sided) for testing the hypothesis that the percentage of responders by GM (sweat reduction >=50%) at Week 12 is equal to 50%

Proportion of responders	P-value (two-sided alpha=0.05)	Exact two-sided 95% Clopper-Pearson confidence interval	Conclusion
[redacted]	[redacted]	[redacted]	The hypothesis that the percentage of responders is equal to [redacted] (proportion of responders equal to [redacted] was not rejected.

1-sample binomial test at a significance level of 5% (two-sided) for testing the hypothesis that the percentage of responders by GM (sweat reduction >=75%) at Week 12 is equal to 25%

Proportion of responders	P-value (two-sided alpha=0.05)	Exact two-sided 95% Clopper-Pearson confidence interval	Conclusion
[redacted]	[redacted]	[redacted]	The hypothesis that the percentage of responders is equal to [redacted] (proportion of responders equal to [redacted]) was rejected.

1-sample binomial test at a significance level of 5% (two-sided) for testing the hypothesis that the percentage of responders by GM (sweat reduction >=90%) at Week 12 is equal to 15%

Proportion of responders	P-value (two-sided alpha=0.05)	Exact two-sided 95% Clopper-Pearson confidence interval	Conclusion
[redacted]	[redacted]	[redacted]	The hypothesis that the percentage of responders is equal to [redacted] (proportion of responders equal to [redacted]) was rejected.

Table 70 Full analysis set (Phase 3a) (FASa)

	Absolute change in HDSS from Baseline to Day 29								
	N	Missing	Mean	SD	Minimum	1st quartile	Median	3rd quartile	Maximum
Treatment 1% GPB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A17. Please explain and justify what would be considered a minimally clinically important difference (MCID) for treatment response for HDSS.

Response: We are not aware of an established MCID for HDSS. A 1-point improvement in HDSS is associated with a 50% reduction in sweat production, while a 2-point improvement corresponds to an 80% reduction.[2]

A18. Please clarify why the change from baseline in median HDSS at day 29 in Hyp1-18/2016 Phase 3a is reported as 0.0 for both trial arms and the p-value suggests a statistically significant difference (p = 0.014; company submission Table 10).

Response: While the median values are the same in the study (between Placebo and GPB 1% cream, essentially meaning in 50 % of patients have a change of HDSS 0.0 by day 29), the samples in total are differently distributed. As you can see in the table below, the 95% Confidence intervals are also different between the groups (mean values are also different). The groups were statistically different, therefore there is a significance. Nonetheless, medians were the same (distribution was different in between groups).

Table 71 Phase 3a: Absolute change in HDSS from Baseline to Day 15 and Day 29 (FASa, N = 171)

	Day 15		Day 29	
HDSS	1% GPB (N = 87)	Placebo (N = 84)	1% GPB (N = 87)	Placebo (N = 84)
Baseline, median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline[b]	[redacted]	[redacted]	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value[g]	[redacted]	[redacted]	[redacted]	[redacted]
Difference to placebo[h] Median	[redacted]		[redacted]	
p-value[g]	[redacted]		[redacted]	

[a] N = 86. [b] Wilcoxon signed rank test with Hahn-Meeker CI.
[c] N = 84. [d] N = 79. [e] N = 83. [f] N = 80.
[g] 2-sided, α = 0.05.
[h] Van Elteren 2-sample test stratified by center; n = 163.
CI = confidence interval, FASa = full analysis set (Phase 3a), GPB = glycopyrronium bromide, HDSS = hyperhidrosis disease severity scale, N = number of patients, n = number of patients in the analysis.

Table 72 Full analysis set (Phase 3a) (FASa)

	Absolute change in HDSS from Baseline to Day 29								
	N	Missing	Mean	SD	Min	1st quartile	Median	3rd quartile	Max
Treatment 1% GPB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A19. The EAG notes that compliance may be an issue within Phase 3b of Hyp1-18/2016, with 150/518 (29.0%) of those enrolled terminating prematurely. The reasons for premature termination are vague in most cases (i.e. "withdrew consent", "lost to follow-up" or "other reasons"). Please can the company discuss the potential reasons for this and the possible impact on the results.

Response: The study sponsors view is that the number of dropouts was low considering the length of the study. The main reasons for dropouts were pregnancies, patients moving home, unwillingness to come to study sites and lack of time. A portion of the Phase 3b study took place during the response to COVID 19.

A20. The EAG could not locate the raw data for the ≥1 HDSS improvement analysis at day 29 outlined in Table 12 of the company submission. Please clarify where these data can be found within the clinical study report or explain why they are not included there (and provide the required data).

Response: This data is from the CSR Study report chapter 11.8.2 *post hoc* analysis

Table 73 Phase 3b: HDSS responders (≥1-point improvement from Baseline) at Weeks 4, 8, 12, 28, 52, and 72 (FASb)

HDSS responders visit	N	Number (%)[a] of Patients	PR	95% CI[b]	p-value[c] (H0: PR = 0.50)
Week 4[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients with missing values were considered non-responders.

[a] Percentages are based on the number of patients in the analysis [b] Clopper-Pearson.

[c] 1-sample binomial test, 2-sided, α = 0.05. [d] Data of newly recruited patients only.

CI = confidence interval, FASb = full analysis set (Phase 3b), H_0 = null hypothesis, HDSS = hyperhidrosis disease severity scale, N = number of patients in the analysis, PR = proportion of responders.

Indirect treatment comparisons

A21. Priority question. ITCs have been performed for HDSS responder outcomes (≥1- and ≥2-point improvements where available). Please provide the rationale for selecting this outcome for ITCs and discuss whether the feasibility of performing ITCs for other outcomes was assessed.

Response: The Hyperhidrosis Disease Severity Scale (HDSS) is a disease-specific, quick, and easily-understood diagnostic tool that provides a qualitative measure of the severity of the patient's condition based on how it affects daily activities.[3] The validity and reliability of the HDSS have been analysed using three studies and have been found to have strong to moderate correlations with the Hyperhidrosis Impact Questionnaire (HHIQ), Dermatology Quality of Life Index (DLQI), and gravimetric sweat production measurements. [4–7]

A response on the HDSS represents a clinically meaningful improvement from the patient's perspective, reflecting both symptom relief and reduced impact on daily functioning. Although not typically used as a formal diagnostic or monitoring tool in UK clinical practice, the HDSS captures the type of subjective assessment that clinicians rely on when evaluating treatment response. Feedback from a UK clinical expert confirmed that objective measures, such as gravimetric sweat assessments, are rarely used in practice. Instead, treatment effectiveness is generally judged based on the patient's own perception of symptom severity. The HDSS is specifically designed to capture this subjective experience, making it highly relevant for comparative effectiveness analyses and ensuring alignment with how treatment response is assessed in real-world UK settings.

Importantly, this endpoint also supports the structure of the economic model used in the evaluation. As described in Section 3.1 of the CS, the HDSS-defined health states align with three of the four economic models identified in the economic SLR.

Additionally, the HDSS responder rate was reported across randomised controlled trials which were identified in the clinical SLR, enabling the benefits of randomisation within the indirect comparisons. In contrast, alternative outcomes such as gravimetric sweat reduction, adverse events, or Dermatology Life Quality Index (DLQI) scores were either reported inconsistently or measured using heterogeneous methodologies, limiting their comparability across studies. As a result, these outcomes were considered less suitable for use in ITCs.

A22. Priority question. Please conduct ITCs for all other outcomes reported in the NICE final scope and not already reported in the company submission.

Response: The NICE final scope listed the following outcomes of interest: disease severity, absolute change in sweat production, response rates, adverse events (AEs), and health-related quality of life (HRQoL).

In PAHH, disease severity is best captured through patient-reported outcomes, as the condition is primarily defined by the patient's subjective experience of excessive sweating and its impact on daily life. The HDSS is the most widely used tool in clinical

trials to measure this, and is designed to assess the functional impact of sweating on daily activities[3]. For this reason, the ITCs were conducted using HDSS-defined response. HDSS response is consistently defined across trials and aligns with how disease severity is assessed in UK clinical practice. It also supports the economic model structure, where treatment benefit is captured through transitions between HDSS health states.

In contrast, ITCs were not performed for absolute change in sweat production, AEs, or HRQoL, due to significant heterogeneity in how these outcomes are measured and reported across the clinical evidence base.

For absolute change in sweat production, although commonly measured using gravimetric methods (e.g., sweat weight in mg per axilla over a fixed time), the specific methodologies vary widely across studies. Differences include the pre-measurement rest period, duration of measurement, environmental controls (e.g., temperature and humidity), and reporting formats, such as mean or median changes, percent reductions from baseline, log-transformed data, or responder thresholds (e.g., ≥50% reduction). While detailed information on the approach, measurement, and reporting of gravimetric assessments is available from the Phase 3a and 3b clinical trials of GPB 1% cream, this level of detail is often lacking for comparator treatments in the published literature. As a result, it is unclear which specific methods or protocols were used for gravimetric assessments in those studies. These inconsistencies limit the feasibility of conducting valid ITCs. Moreover, gravimetric assessment is not used in routine UK clinical practice, and clinical experts have confirmed that treatment decisions are made based on patients' subjective perceptions (aligned with the HDSS). Notably, studies have shown a correlation between HDSS response and sweat production, with a two-point HDSS improvement associated with approximately an 80% reduction in sweat production, and a one-point improvement linked to a 50% reduction.[2,7,8]

AEs were also not included in the ITCs due to inconsistent definitions and reporting across trials. Some studies did not report AEs at all, while others reported only treatment-emergent events or included all AEs regardless of causality. Furthermore, there was variability in how AEs were grouped (e.g., by system organ class or

severity), and the follow-up periods used for safety monitoring were often unclear or inconsistent. In many cases, insufficient methodological detail was provided to allow for meaningful adjustment or comparison using the GPB 1% cream data.

HRQoL outcomes were reported using a variety of instruments across studies, including the DLQI, HidroQoL, SF-36, and EQ-5D. Studies varied in how they reported results, such as total score, change from baseline, or proportion of patients achieving a minimally important difference. This heterogeneity in measurement and reporting further limited the feasibility of conducting a reliable ITC based on HRQoL data.

In summary, while several outcomes were identified in the NICE scope, only HDSS response was suitable for indirect comparison due to its consistent use, clinical relevance, alignment with UK practice, and compatibility with the model structure. The remaining outcomes could not be robustly compared due to methodological variability and insufficient reporting detail across the evidence base.

A23. Priority question. Please conduct fully adjusted MAICs using the methods outlined in NICE DSU TSD18[1] for the comparisons of GPB 1% cream versus antimuscarinics and GPB 1% cream versus botulinum toxin type A using the studies in the ITCs reported in the CS (Hyp1-18/2016 Phase 3a for GPB 1% cream, Schollhammer *et al*. (2015) for antimuscarinics and Lowe *et al.* (2007) for botulinum toxin) and ensure all reported baseline characteristics are balanced between the studies.[2, 3] Please provide the following:

a) **the baseline characteristics including the effective sample size after matching;**
b) **the distribution of participant weights within the adjusted GPB 1% cream populations;**
c) the results for ⩾2 HDSS improvement and ⩾1 HDSS improvement;
d) **the results for change in sweat production; and**
e) **change in DLQI.**

In particular, the EAG's clinical experts consider the following to be potentially important prognostic factors: age, sex and baseline sweat production.

Please comment on any factors that could not be adjusted for and the impact this lack of adjustment is expected to have on the results.

Please ensure that results of the MAICs are included in the economic model and explored in scenario analyses.

Response: Matching-Adjusted Indirect Comparisons (MAICs) are typically used when individual patient data (IPD) are available for one treatment and only aggregate-level data are available for the comparator.[9] By reweighting the IPD to align with the baseline characteristics of the comparator trial, MAICs can adjust for differences in effect modifiers and prognostic factors, which is particularly useful when there are substantial cross-trial differences in patient populations.

However, as outlined in Section 2.9 of the CS, more complex methods such as MAIC were assessed and determined to be either infeasible or unlikely to produce more reliable estimates of relative efficacy. Instead, Bucher ITCs were conducted using readily available aggregate data from the Phase 3a trial of GPB 1% cream, Schollhammer et al. (2015),[10] and Lowe et al. (2007)[8].

The Bucher method was selected as it preserves the benefits of randomisation, minimises bias, and allows for a transparent and straightforward comparison across studies with a shared placebo comparator. Importantly, the evidence network in this setting is well connected through this common comparator, supporting the use of the Bucher ITC method.

Specifically, a MAIC using data from Schollhammer et al. (2015) would not be viable, as this study evaluated oxybutynin in a broader HH population, not limited to individuals with severe PAHH. Although most participants in the study had severe disease (90% in the oxybutynin arm, 93% in the placebo arm) and axillary involvement (75% and 70%, respectively), a significant proportion of patients had less severe disease or different site involvement. In contrast, the GPB 1% cream trial exclusively included patients with severe PAHH. These population differences cannot be adequately adjusted for using reweighting methods, making a MAIC unsuitable in this case.

MAICs were also not pursued in the botulinum toxin comparison using the Lowe et al. (2007) data. The study populations in Lowe et al. (2007) and the GPB 1% cream Phase 3a trial are comparable in terms of baseline characteristics and eligibility criteria, and no major differences in effect modifiers are expected – see Table 74. Therefore, the Bucher ITC approach is appropriate and applying MAIC methodology would introduce additional complexity without improving the validity or reliability of the comparison. MAICs are designed to adjust for differences in baseline characteristics between trials. As the trial populations are already aligned with similar baseline characteristics and the same inclusion/exclusion criteria, no adjustment is needed. Notably, a key consideration in comparing botulinum toxin with GPB 1% cream is the need to account for the waning effect of botulinum toxin over time. This presents a methodological challenge that would apply equally to either a Bucher ITC or a MAIC and does not support a preference for one method over the other in this regard.

Table 74: Comparison of inclusion/exclusion criteria and baseline characteristics between the Phase 3a clinical trial for GPB 1% cream and Lowe et al. (2007) for botulinum toxin

Study	Key inclusion criteria	Key exclusion criteria	Age (yrs)	% primary HH	Median baseline HDSS	Baseline gravimetric sweat production	DLQI	% male	% female
Abels et al. (2021), Phase 3a GPB 1% cream	Age 18 to 65 years, BMI of 18–32 kg m^{-2}, severe PAHH characterized by HDSS score of 3 or 4, resting axillary sweat production in each axilla of >50 mg in 5 min	Hypersensitivity to GPB, secondary HH, previous surgical treatment for HH, botulinum toxin treatment in the 4 months prior to the study	For GPB and placebo, years: Mean (SD): 37.4 (11.9) and 37.8 (12.3) Range: 18–65 and 18–65	[redacted]	For GPB and placebo, median (range): [redacted] and [redacted]	For GPB and placebo, mean (SD), mg produced in 5 min: [redacted] and [redacted]	For GPB and placebo, median (range): [redacted]	[redacted] for both arms	[redacted] for both arms
Lowe et al. (2007)	At least 18 years old with persistent bilateral PAHH, a HDSS score of 3 or 4,baseline gravimetric measurement of spontaneous resting sweat production of at least 50 mg/axilla, measured over 5 minutes at room temperature	Secondary hyperhidrosis or a medical condition that might interfere with BoNTA treatment	mean (range): vehicle=[redacted]	[redacted]	mean HDSS: Vehicle = [redacted]	mg/5min Vehicle = [redacted]	Vehicle = [redacted]	Vehicle = [redacted]	Vehicle = [redacted]

Additionally, as outlined in the response to the clarification question submitted to NICE on 30th May 2025, Leith Healthcare does not have direct access to the IPD from the GPB 1% cream clinical trials. While there is a route to the IPD through the data holder, any access would require a formal request. Notably, no further analyses beyond those included in the clinical study report (CSR) were requested by regulators.

A24. Priority question. Please conduct fully adjusted MAICs using the methods outlined in NICE DSU TSD18 for the comparisons of GPB 1% cream versus antimuscarinics and GPB 1% cream versus botulinum toxin type A using the Phase 3b study to inform GPB 1% cream and the relevant comparator studies in the ITCs reported in the CS ensuring all reported baseline characteristics are balanced between the studies.

Please provide the following:

a) **the baseline characteristics including the effective sample size after matching;**
b) **the distribution of participant weights within the adjusted GPB 1% cream populations;**
c) the results for ⩾2 HDSS improvement and ⩾1 HDSS improvement.

Please comment on any factors that could not be adjusted for and the impact this lack of adjustment is expected to have on the results.

Please ensure that results of the MAICs are included in the economic model and explored in scenario analyses.

Response: As outlined in the response to Clarification Question A24, more complex methods such as MAICs were assessed but found to be either infeasible or unlikely to produce more robust estimates of relative efficacy. The rationale and conclusions set out in that response remain applicable and consistent for this question.

However, in this instance, the EAG have specifically requested an unanchored MAIC using single-arm data from the Phase 3b clinical trial of GPB 1% cream. Unanchored MAICs require particularly strong and untestable assumptions e.g., that all relevant prognostic factors and effect modifiers are known, accurately measured, and fully

adjusted for in the analysis. These assumptions cannot be verified and introduce a high risk of bias.

Unlike anchored comparisons, which benefit from a shared comparator arm to mitigate residual confounding, unanchored comparisons do not control for unobserved differences between studies. As a result, they are inherently more uncertain and less reliable.

In line with NICE Technical Support Document 18, unanchored population-adjustment methods are considered problematic and are not recommended when anchored approaches are available. Given that the Bucher ITCs included in the submission use a common comparator and draw on randomised, controlled data, they provide a more robust and appropriate basis for indirect comparison in this context.

A25. Please provide a list of studies that were included in the SLR but subsequently excluded from the ITCs (i.e. outlining which of the 80 publications mentioned in Appendix B.2.2 were not considered relevant for the ITCs), including the rationale for the exclusion of each from ITCs.

Response: Of the 80 publications identified in the clinical SLR, four studies were included in the ITC. These included the Abels *et al., 2021* and Szeimies *et al.,* 2022 GPB 1% cream trials presented in the CS, [11,12] the Lowe *et al.,* 2007 Botox study[8] and the Schollhammer *et al.,* 2015 oxybutynin study.[10] The remaining 76 publications were excluded from the ITCs as they were not representative of UK clinical practice, not representative of the UK population, did not include placebo/no treatment as a comparator, or did not include HDSS as an efficacy outcome. These studies and their reasons for exclusion are outlined in Table 75.

Table 75: Reasons why 76 studies identified in the clinical SLR were not used in the ITCs

Publication Year	Author	Title	Reason for exclusion in the ITC
2024	Grove, Gabriela Lladó; Togsverd-Bo, Katrine; Zachariae, Claus; Haedersdal, Merete	Botulinum toxin A versus microwave thermolysis for primary axillary hyperhidrosis: A randomized controlled trial.	This study compared Botulinum toxin A with microwave thermolysis. To perform an ITC, the Company required studies that include a placebo arm.
2015	An, Jee Soo; Hyun Won, Chong; Si Han, Ji; Park, Hyun Sun; Seo, Kyle K.	Comparison of onabotulinumtoxina and rimabotulinumtoxinb for the treatment of axillary hyperhidrosis.	This study compared onabotulinumtoxina with rimabotulinumtoxinb. To perform an ITC, the Company required studies that include a placebo arm.
2022	Yokozeki, Hiroo; Fujimoto, Tomoko; Wanatabe, Shunsuke; Ogawa, Shuhei; Fujii, Chie	Topical glycopyrronium tosylate in Japanese patients with primary axillary hyperhidrosis: A randomized, double-blind, vehicle-controlled study.	Although tosylate cloth contains glycopyrronium, it is not representative of UK clinical practice. Additionally, the study was performed on a Japanese population of patients which is not considered representative of the UK population.
2020	Garcia-Souto, Fernando; Del Boz, Javier; Polo-Padillo, Juan	Adjusting oral glycopyrrolate medication for hyperhidrosis to reflect seasonal temperature variations.	Oral glycopyrrolate is not representative of UK clinical practice. Furthermore, this study did not contain a placebo arm, which was required to perform an ITC.
2020	Lynch, Olwyn E.; Aherne, T.; Gibbons, J.; Boland, M. R.; Ryan, É J.; Boyle, E.; Egan, B.; Tierney, S.	Five-year follow-up of patients treated with intra-dermal botulinum toxin for axillary hyperhidrosis.	This study focused on the QoL impact of botulinum toxin, assessed using DLQI, rather than the efficacy of botulinum toxin using HDSS. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.

Publication Year	Author	Title	Reason for exclusion in the ITC
2020	Kirsch, Brandon; Smith, Stacy; Cohen, Joel; DuBois, Janet; Green, Lawrence; Baumann, Leslie; Bhatia, Neal; Pariser, David; Liu, Ping-Yu; Chadha, Deepak; Walker, Patricia	Efficacy and safety of topical sofpironium bromide gel for the treatment of axillary hyperhidrosis: A phase II, randomized, controlled, double-blinded trial.	Although sofpironium bromide contains glycopyrronium, it is not representative of UK clinical practice.
2024	Castiglione, Luca; Murariu, Marius; Boeriu, Estera; Enatescu, Ileana	Assessing Botulinum Toxin Effectiveness and Quality of Life in Axillary Hyperhidrosis: A One-Year Prospective Study.	This study focused on Botulinum toxin with no comparator. To perform an ITC, the Company required studies that include a placebo arm.
2022	Fujimoto, Tomoko; Okatsu, Hiromichi; Miyama, Hiroshi	Two-week prospective observational study of 5% sofpironium bromide gel in Japanese patients with primary axillary hyperhidrosis.	Although sofpironium contains glycopyrronium, it is not representative of UK clinical practice. Additionally, the study was performed on a Japanese population of patients which is not considered representative of the UK population.
2018	Nguyen, Nicholas V.; Gralla, Jane; Abbott, James; Bruckner, Anna L.	Oxybutynin 3% gel for the treatment of primary focal hyperhidrosis in adolescents and young adults.	Oxybutynin gel is not reflective of UK clinical practice.
2015	Mehrotra, Shailly; Schmith, Virginia D.; Dumitrescu, Teodora Pene; Gobburu, Jogarao	Pharmacometrics-guided drug development of antihyperhidrosis agents.	Although glycopyrrolate cloth contains glycopyrronium, it is not representative of UK clinical practice.
2023	Shayesteh, Alexander; Boman, Antonia; Hawas, Emil; Carlberg, Bo	Reconstituted and frozen botulinum toxin A is as effective and safe as fresh for treating axillary hyperhidrosis: A retrospective study.	This study compared fresh with thawed botulinum toxin A. To perform an ITC, the Company required studies that include a placebo arm.
2023	Siri-Archawawat, Doungkamol; Tawanwongsri, Weeratian	Low-Dose onabotulinumtoxina using Seven-Point Pattern	This study compared different doses of onabotulinumtoxin A. To perform an ITC, the

Publication Year	Author	Title	Reason for exclusion in the ITC
		Intradermal Injections in Patients with Moderate-to-intolerable Primary Axillary Hyperhidrosis: A Single-Blinded, Side-by-Side Randomized Trial.	Company required studies that include a placebo arm.
2017	Millán-Cayetano, José Francisco; Del Boz, Javier; Rivas-Ruiz, Francisco; Blázquez-Sánchez, Nuria; Hernández Ibáñez, Carlos; de Troya-Martín, Magdalena	Oral oxybutynin for the treatment of hyperhidrosis: outcomes after one-year follow-up.	This study was a retrospective analysis on use of oxybutynin with no comparator. To perform an ITC, the Company required studies that include a placebo arm.
2020	Trindade de Almeida, Ada Regina; Noriega, Leandro Fonseca; Bechelli, Liliana; Suárez, Maria Victoria	Randomized Controlled Trial Comparing the Efficacy and Safety of Two Injection Techniques of incobotulinumtoxina for Axillary Hyperhidrosis.	This study compared Incobotulinumtoxin A injection techniques. To perform an ITC, the Company required studies that include a placebo arm.
2002	Dressler, Dirk; Adib Saberi, Fereshte; Benecke, Reiner	Botulinum toxin type B for treatment of axillar hyperhidrosis.	This study compared Neurobloc/MyoBloc with Botox. To perform an ITC, the Company required studies that include a placebo arm.
2022	Bérard, Mathilde; Leducq, Sophie; Laribi, Kamel; Samaran, Romain; Maillard, Hervé	Factors associated with efficacy of botulinum toxin a injections in primary axillary hyperhidrosis: A retrospective study of ninety patients.	This study was a retrospective analysis on use of botulinum toxin A with no comparator. To perform an ITC, the Company required studies that include a placebo arm.
2022	Lee, Dong Geon; Kim, Jung Eun; Lee, Woo Shun; Kim, Moon-Bum; Huh, Chang-Hun; Lee, Yang Won; Choi, Gwang Seong; Lee, Jee-Bum; Yu, Dong Soo; Shin, Min Kyung; Roh, Mi Ryung; Ahn, Hyo Hyun; Kim, Won-Serk; Lee, Jong	A Phase 3, Randomized, Multi-center Clinical Trial to Evaluate the Efficacy and Safety of Neu-bont/A in Treatment of Primary Axillary Hyperhidrosis.	This study was performed in a Korean population and was not considered representative of the UK population.

Publication Year	Author	Title	Reason for exclusion in the ITC
	Hee; Park, Kui Young; Park, Jin; Lee, Weon Ju; Park, Mi Youn; Kang, Hoon		
2019	Glaser, Dee Anna; Hebert, Adelaide A.; Nast, Alexander; Werschler, William P.; Green, Lawrence; Mamelok, Richard D.; Quiring, John; Drew, Janice; Pariser, David M.	A 44-Week Open-Label Study Evaluating Safety and Efficacy of Topical Glycopyrronium Tosylate in Patients with Primary Axillary Hyperhidrosis.	Although tosylate cloth contains glycopyrronium, it is not representative of UK clinical practice.
2014	Wolosker, Nelson; Teivelis, Marcelo Passos; Krutman, Mariana; de Paula, Rafael Pessanha; Kauffman, Paulo; de Campos, José Ribas M.; Puech-Leão, Pedro	Long-term results of the use of oxybutynin for the treatment of axillary hyperhidrosis.	This study was a retrospective analysis on use of oxybutynin with no comparator. To perform an ITC, the Company required studies that include a placebo arm.
2001	Heckmann, M.; Ceballos-Baumann, A. O.; Plewig, G.	Botulinum toxin A for axillary hyperhidrosis (excessive sweating).	This study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2019	Pariser, David M.; Hebert, Adelaide A.; Drew, Janice; Quiring, John; Gopalan, Ramanan; Glaser, Dee Anna	Topical Glycopyrronium Tosylate for the Treatment of Primary Axillary Hyperhidrosis: Patient-Reported Outcomes from the ATMOS-1 and ATMOS-2 Phase III Randomized Controlled Trials.	Although tosylate cloth contains glycopyrronium, it is not representative of UK clinical practice.
2010	Dressler, Dirk	Comparing Botox and Xeomin for axillar hyperhidrosis.	This study compared Botox with Xeomin. To perform an ITC, the Company required studies that include a placebo arm.

Publication Year	Author	Title	Reason for exclusion in the ITC
2018	Varella, Andrea Yasbek Monteiro; Fukuda, Juliana Maria; Teivelis, Marcelo Passos; Pinheiro, Lucas Lembrança; Mendes, Cynthia de Almeida; Kauffman, Paulo; Campos, José Ribas Milanez de; Wolosker, Nelson	Combination of topical agents and oxybutynin as a therapeutic modality for patients with both osmidrosis and hyperhidrosis.	This study compared oxybutynin with topical agents. To perform an ITC, the Company required studies that include a placebo arm.
2013	Rosell, Karolina; Hymnelius, Kristina; Swartling, Carl	Botulinum toxin type A and B improve quality of life in patients with axillary and palmar hyperhidrosis.	This study compared Botulinum toxin type A with Botulinum toxin type B. To perform an ITC, the Company required studies that include a placebo arm.
2019	Glaser, Dee Anna; Hebert, Adelaide A.; Nast, Alexander; Werschler, William P.; Green, Lawrence; Mamelok, Richard; Drew, Janice; Quiring, John; Pariser, David M.	Topical glycopyrronium tosylate for the treatment of primary axillary hyperhidrosis: Results from the ATMOS-1 and ATMOS-2 phase 3 randomized controlled trials.	Although tosylate cloth contains glycopyrronium, it is not representative of UK clinical practice.
1999	Heckmann, M.; Breit, S.; Ceballos-Baumann, A.; Schaller, M.; Plewig, G.	Side-controlled intradermal injection of botulinum toxin A in recalcitrant axillary hyperhidrosis.	This study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2020	Rummaneethorn, Paisal; Chalermchai, Thep	A comparative study between intradermal botulinum toxin A and fractional microneedle radiofrequency (FMR) for the treatment of primary axillary hyperhidrosis.	This study compared botulinum toxin A with FMR. To perform an ITC, the Company required studies that include a placebo arm.

Publication Year	Author	Title	Reason for exclusion in the ITC
2017	Budamakuntla, Leelavathy; Loganathan, Eswari; George, Anju; Revanth, B. N.; Sankeerth, V.; Sarvjnamurthy, Sacchidananda Aradhya	Comparative Study of Efficacy and Safety of Botulinum Toxin A Injections and Subcutaneous Curettage in the Treatment of Axillary Hyperhidrosis.	This study compared Botulinum Toxin A with curettage. To perform an ITC, the Company required studies that include a placebo arm.
1999	Schnider, P.; Binder, M.; Kittler, H.; Birner, P.; Starkel, D.; Wolff, K.; Auff, E.	A randomized, double-blind, placebo-controlled trial of botulinum A toxin for severe axillary hyperhidrosis.	This study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
1998	Naumann, M.; Hofmann, U.; Bergmann, I.; Hamm, H.; Toyka, K. V.; Reiners, K.	Focal hyperhidrosis: effective treatment with intracutaneous botulinum toxin.	This study investigated botulinum toxin with no comparator. To perform an ITC, the Company required studies that included a placebo arm. Furthermore, this study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2018	Lueangarun, Suparuj; Sermsilp, Chairat; Tempark, Therdpong	Topical Botulinum Toxin Type A Liposomal Cream for Primary Axillary Hyperhidrosis: A Double-Blind, Randomized, Split-Site, Vehicle-Controlled Study.	This study used Botulinum Toxin Type liposomal cream and is not reflective of UK clinical practice.
2005	Nelson, L.; Bachoo, P.; Holmes, J.	Botulinum toxin type B: a new therapy for axillary hyperhidrosis.	This study investigated Botulinum toxin type B with no comparator. To perform an ITC, the Company required studies that included a placebo arm. Furthermore, this study did not

Publication Year	Author	Title	Reason for exclusion in the ITC
			include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2003	Lowe, Phillipa L.; Cerdan-Sanz, Suzanne; Lowe, Nicholas J.	Botulinum toxin type A in the treatment of bilateral primary axillary hyperhidrosis: efficacy and duration with repeated treatments.	This study investigated Botulinum toxin type A with no comparator in an open-label study. To perform an ITC, the Company required studies that include a placebo arm.
2001	Schnider, P.; Moraru, E.; Kittler, H.; Binder, M.; Kranz, G.; Voller, B.; Auff, E.	Treatment of focal hyperhidrosis with botulinum toxin type A: long-term follow-up in 61 patients.	This study investigated botulinum toxin type A with no comparator in an open-label study. To perform an ITC, the Company required studies that include a placebo arm
2010	Paul, Anna; Kranz, Gottfried; Schindl, Andreas; Kranz, Georg S.; Auff, Eduard; Sycha, Thomas	Diode laser hair removal does not interfere with botulinum toxin A treatment against axillary hyperhidrosis.	This study compared botulinum toxin A with laser and botulinum toxin A. To perform an ITC, the Company required studies that included a placebo arm. Furthermore, this study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2017	Pariser, David M.; Krishnaraja, Janakan; Tremblay, Thomas M.; Rubison, R. Michael; Love, Ted W.; McGraw, Benjamin F.	Randomized, Placebo- and Active-Controlled Crossover Study of the Safety and Efficacy of THVD-102, a Fixed-dose Combination of Oxybutynin and	THVD-02 is a combination of pilocarpine and oxybutynin which is not reflective of UK clinical practice.

Publication Year	Author	Title	Reason for exclusion in the ITC
		Pilocarpine, in Subjects With Primary Focal Hyperhidrosis.	
2018	Nasir, A.; Bissonnette, R.; Maari, C.; DuBois, J.; Pene Dumitrescu, T.; Haddad, J.; Yamaguchi, Y.; Dalessandro, M.	A phase 2a randomized controlled study to evaluate the pharmacokinetic, safety, tolerability and clinical effect of topically applied Umeclidinium in subjects with primary axillary hyperhidrosis.	Umeclidian is not representative of UK clinical practice.
2002	Wollina, Uwe; Karamfilov, Theodor; Konrad, Helga	High-dose botulinum toxin type A therapy for axillary hyperhidrosis markedly prolongs the relapse-free interval.	This study investigated botulinum toxin A with no comparator in an open stud. To perform an ITC, the Company required studies that include a placebo arm.
2007	Talarico-Filho, Sérgio; Mendonça DO Nascimento, Maurício; Sperandeo DE Macedo, Fernando; DE Sanctis Pecora, Carla	A double-blind, randomized, comparative study of two type A botulinum toxins in the treatment of primary axillary hyperhidrosis.	This study compared Botox with Dysport. To perform an ITC, the Company required studies that included a placebo arm. Furthermore, this study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2013	Ibrahim, Omer; Kakar, Rohit; Bolotin, Diana; Nodzenski, Michael; Disphanurat, Wareeporn; Pace, Natalie; Becker, Lauren; West, Dennis P.; Poon, Emily; Veledar, Emir; Alam, Murad	The comparative effectiveness of suction-curettage and onabotulinumtoxin-A injections for the treatment of primary focal axillary hyperhidrosis: a randomized control trial.	This study compared onabotulinumtoxin-A with curettage. To perform an ITC, the Company required studies that include a placebo arm. Furthermore, this study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness

Publication Year	Author	Title	Reason for exclusion in the ITC
			of GPB 1% cream could not be robustly compared using an ITC.
2005	Heckmann, Marc; Plewig, Gerd	Low-dose efficacy of botulinum toxin A for axillary hyperhidrosis: a randomized, side-by-side, open-label study.	This study compared doses of botulinum toxin. To perform an ITC, the Company required studies that include a placebo arm. Furthermore, this study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2025	Elshabory, Osama; Mohamed, Hassan Abou Khodair; Zaky, Mohamed; Elsaie, Mohamed L.	Comparative study between fractional laser assisted drug delivery of botulinum toxin versus botulinum toxin injection in primary palmar and axillary hyperhidrosis.	This study compared botulinum toxin with laser and botulinum toxin. To perform an ITC, the Company required studies that include a placebo arm. Furthermore, this study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2025	Pariser, David; Glaser, Dee Anna; Del Rosso, James; Bhatia, Neal; Hooper, Deirdre; Nestor, Mark S.; Smith, Stacy; Schlessinger, Joel; Hebert, Adelaide; Walker, Patricia S.	Sofpironium topical gel, 12.45%, for the treatment of axillary hyperhidrosis: pooled efficacy and safety results from 2 phase 3 randomized, controlled, double-blind studies.	Although sofpironium bromide contains glycopyrronium, it is not representative of UK clinical practice.
2003	Naumann, M.; Lowe, N. J.; Kumar, C. R.; Hamm, H.	Botulinum toxin type a is a safe and effective treatment for	This study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS

Publication Year	Author	Title	Reason for exclusion in the ITC
		axillary hyperhidrosis over 16 months: a prospective study.	data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2015	Brehmer, Franziska; Lockmann, Anike; Grönemeyer, Lisa-Lena; Kretschmer, Lutz; Schön, Michael P.; Thoms, Kai-Martin	Repetitive injections of botulinum toxin A continuously increase the duration of efficacy in primary axillary hyperhidrosis: a retrospective analysis in 101 patients.	This study investigated botulinum toxin A with no comparator. To perform an ITC, the Company required studies that include a placebo arm. Furthermore, this study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2013	Lecouflet, Marie; Leux, Christophe; Fenot, Marion; Célerier, Philippe; Maillard, Hervé	Duration of efficacy increases with the repetition of botulinum toxin A injections in primary axillary hyperhidrosis: a study in 83 patients.	This study investigated botulinum toxin A with no comparator. To perform an ITC, the Company required studies that include a placebo arm. Furthermore, this study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2014	Montaser-Kouhsari, Laleh; Zartab, Hamed; Fanian, Ferial; Noorian, Negin; Sadr, Bardia; Nassiri-Kashani, Mansour; Firooz, Alireza	Comparison of intradermal injection with iontophoresis of abobotulinum toxin A for the treatment of primary axillary hyperhidrosis: a randomized, controlled trial.	This study compared abobotulinum toxin A with abobotulinum toxin A and iontophoresis. To perform an ITC, the Company required studies that include a placebo arm. Furthermore, this study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS

Publication Year	Author	Title	Reason for exclusion in the ITC
			data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2005	Solish, Nowell; Benohanian, Antranik; Kowalski, Jonathan W.	Prospective open-label study of botulinum toxin type A in patients with axillary hyperhidrosis: effects on functional impairment and quality of life.	This study investigated botulinum toxin type A with no comparator. To perform an ITC, the Company required studies that include a placebo arm. Furthermore, this study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2013	Müller, C.; Berensmeier, A.; Hamm, H.; Dirschka, T.; Reich, K.; Fischer, T.; Rzany, B.	Efficacy and safety of methantheline bromide (Vagantin(®)) in axillary and palmar hyperhidrosis: results from a multicenter, randomized, placebo-controlled trial.	Methantheline bromide is not representative of UK clinical practice.
2012	Güleç, A. T.	Dilution of botulinum toxin A in lidocaine vs. In normal saline for the treatment of primary axillary hyperhidrosis: a double-blind, randomized, comparative preliminary study.	This study compared botulinum toxin A with botulinum toxin A and lidocaine. To perform an ITC, the Company required studies that include a placebo arm. Furthermore, this study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.

Publication Year	Author	Title	Reason for exclusion in the ITC
2000	Karamfilov, T.; Konrad, H.; Karte, K.; Wollina, U.	Lower relapse rate of botulinum toxin A therapy for axillary hyperhidrosis by dose increase.	This study investigated botulinum toxin A with no comparator in an open study. To perform an ITC, the Company required studies that include a placebo arm.
2003	Goodman, Greg	Diffusion and short-term efficacy of botulinum toxin A after the addition of hyaluronidase and its possible application for the treatment of axillary hyperhidrosis.	This study compared botulinum toxin A with botulinum toxin A and hyaluronic acid. To perform an ITC, the Company required studies that include a placebo arm. Furthermore, this study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2002	Odderson, Ib R.	Long-term quantitative benefits of botulinum toxin type A in the treatment of axillary hyperhidrosis.	This study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2007	Vadoud-Seyedi, J.; Simonart, T.	Treatment of axillary hyperhidrosis with botulinum toxin type A reconstituted in lidocaine or in normal saline: a randomized, side-by-side, double-blind study.	This study compared botulinum toxin type A with botulinum toxin type A and lidocaine. To perform an ITC, the Company required studies that include a placebo arm. Furthermore, this study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.

Publication Year	Author	Title	Reason for exclusion in the ITC
2007	Glogau, Richard G.	Topically applied botulinum toxin type A for the treatment of primary axillary hyperhidrosis: results of a randomized, blinded, vehicle-controlled study.	This study used topical botulinum toxin type A which is not reflective of UK clinical practice.
2002	Naumann, M. K.; Hamm, H.; Lowe, N. J.	Effect of botulinum toxin type A on quality of life measures in patients with excessive axillary sweating: a randomized controlled trial.	This study focused on the QoL impact of botulinum toxin type A, rather than the efficacy of botulinum toxin using HDSS. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2006	Hanlon, L.; Cahill, R.; Barry, M. C.	Prospective evaluation of the efficacy of dermal botulinium toxin for primary axillary hyperhidrosis.	This study investigated botulinium toxin with no comparator. To perform an ITC, the Company required studies that include a placebo arm. Furthermore, this study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2001	Naumann, M.; Lowe, N. J.	Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomised, parallel group, double blind, placebo controlled trial.	This study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.

Publication Year	Author	Title	Reason for exclusion in the ITC
2024	Antón Andrés, M.J.; Candau Pérez, E.D.; Bermejo de la Fuente, M.P.	Treatment of Primary Axillary Hyperhidrosis with Two Doses of Botulinum Toxin A—Observational Study	This study investigated Botulinum Toxin A with no comparator. To perform an ITC, the Company required studies that include a placebo arm. Furthermore, this study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2023	Grove, G.L.; Togsverd-Bo, K.; Haedersdal, M.	Long-term efficacy of microwave thermolysis and botulinum toxin a for axillary hyperhidrosis - a randomized controlled trial	This study compared botulinum toxin with microwave thermolysis. To perform an ITC, the Company required studies that include a placebo arm.
2021	Fujimoto, T.; Abe, Y.; Igarashi, M.; Ishikoh, A.; Omi, T.; Kanda, H.; Kitahara, H.; Kinoshita, M.; Nakasu, I.; Hattori, N.; Horiuchi, Y.; Maruyama, R.; Mizutani, H.; Murakami, Y.; Watanabe, C.; Kume, A.; Hanafusa, T.; Hamaguchi, M.; Yoshioka, A.; Egami, Y.; Matsuo, K.; Matsuda, T.; Akamatsu, M.; Yorozuya, T.; Takayama, S.; Yokozeki, H.	A phase III, 52-week, open-label study to evaluate the safety and efficacy of 5% sofpironium bromide (BBI-4000) gel in Japanese patients with primary axillary hyperhidrosis	Although sofpironium bromide contains glycopyrronium, it is not representative of UK clinical practice. Additionally, this study was performed in a Japanese population of patients which is not representative of the UK population.
2021	Ibrahim, D.A.S.; Elbasiouny, M.S.; Samy, N.A.; Elwakil, T.F.A.	Treatment of primary axillary hyperhidrosis with diode laser 980 nm versus Botulinum Toxin A injection	This study compared Botulinum Toxin A with laser therapy. To perform an ITC, the Company required studies that include a placebo arm.
2021	Yokozeki, H.; Fujimoto, T.; Abe, Y.; Igarashi, M.; Ishikoh, A.; Omi, T.; Kanda, H.; Kitahara, H.; Kinoshita, M.; Nakasu, I.; Hattori, N.; Horiuchi, Y.; Maruyama, R.;	A phase 3, multicenter, randomized, double-blind, vehicle-controlled, parallel-group study of 5% sofpironium bromide	Although sofpironium bromide contains glycopyrronium, it is not representative of UK clinical practice. Additionally, this study was

Publication Year	Author	Title	Reason for exclusion in the ITC
	Mizutani, H.; Murakami, Y.; Watanabe, C.; Kume, A.; Hanafusa, T.; Hamaguchi, M.; Yoshioka, A.; Egami, Y.; Matsuo, K.; Matsuda, T.; Akamatsu, M.; Yorozuya, T.; Takayama, S.	(BBI-4000) gel in Japanese patients with primary axillary hyperhidrosis	performed in a Japanese population of patients which is not representative of the UK.
2020	del Boz Gonzalez, J.; Rodríguez Barón, D.; Millán-Cayetano, J.F.; de Troya Martin, M.	Tolerance of oral oxybutynin in the treatment of hyperhidrosis	This study investigated oxybutynin with no comparator. To perform an ITC, the Company required studies that include a placebo arm. Furthermore, this study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2020	Almeida, A.R.T.; Ferrari, F.; Restrepo, M.V.S.; Rocha, V.B.	Oxybutynin in primary hyperhidrosis: A long-term real-life study	This study investigated oxybutynin with no comparator. To perform an ITC, the Company required studies that include a placebo arm. Furthermore, this study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2020	Glaser, D.A.; Hebert, A.; Gopalan, R.; Drew, J.; Pariser, D.	Short- and long-term efficacy and safety of glycopyrronium cloth for the treatment of primary axillary hyperhidrosis	Although tosylate cloth contains glycopyrronium, it is not representative of UK clinical practice.
2019	Berthin, C.; Maillard, H.	Duration of efficacy increases with the repetition of botulinum toxin a injections in primary	This study investigated Botulinum Toxin A with no comparator. To perform an ITC, the Company required studies that include a placebo arm. Furthermore, this study did not

Publication Year	Author	Title	Reason for exclusion in the ITC
		axillary hyperhidrosis: A 15-year study in 117 patients	include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2018	Pariser, D.; Hebert, A.; Nast, A.; Werschler, W.; Shideler, S.; Green, L.; Mamelok, R.; Quiring, J.; Drew, J.; Glaser, D.A.	Glycopyrronium tosylate for the treatment of primary axillary hyperhidrosis: Previous treatment analyses from the ATMOS-1 and ATMOS-2 phase 3 randomized controlled trials	Although tosylate cloth contains glycopyrronium, it is not representative of UK clinical practice.
2016	Baker, D.M.	Topical glycopyrrolate reduces axillary hyperhidrosis	Although glycopyrrolate spray contains glycopyrronium, it is not representative of UK clinical practice.
2013	Dressler, D.; Adib Saberi, F.	Towards a dose optimisation of botulinum toxin therapy for axillary hyperhidrosis: Comparison of different Botox® doses	This study compared Botox doses. To perform an ITC, the Company required studies that include a placebo arm.
2013	Ibrahim, O.; West, D.; Veledar, E.; Becker, L.; Alam, M.; Kakar, R.	Comparative effectiveness of suction-curettage and onabotulinumtoxin-A injection for the treatment of primary focal axillary hyperhidrosis	This study compared onabotulinumtoxin-A with curettage. To perform an ITC, the Company required studies that include a placebo arm.
2006	Connor, K.M.; Cook, J.L.; Davidson, J.R.T.	Botulinum toxin treatment of social anxiety disorder with hyperhidrosis: A placebo-controlled double-blind trial	This study included 8 weeks open-label paroxetine alongside Botulinum toxin or vehicle injection. To perform an ITC, the Company required studies that include a placebo arm. Furthermore, this study focused

Publication Year	Author	Title	Reason for exclusion in the ITC
			on a population of patients that had social anxiety disorder.
2003	Campanati, A.; Penna, L.; Guzzo, T.; Menotta, L.; Silvestri, B.; Lagalla, G.; Gesuita, R.; Offidani, A.	Quality-of-life assessment in patients with hyperhidrosis before and after treatment with botulinum toxin: Results of an open-label study	This study investigated just botulinum toxin and no comparator in an open-label study. To perform an ITC, the Company required studies that include a placebo arm.
2024	Eid, RO; Shaarawi, E; Hegazy, RA; Hafez, V	Long-term efficacy of fractional microneedle radiofrequency versus botulinum toxin-A in primary axillary hyperhidrosis: a randomized controlled trial	This study compared botulinum toxin-A with FMR. To perform an ITC, the Company required studies that include a placebo arm.
2005	Baumann, L; Slezinger, A; Halem, M; Vujevich, J; Martin, LK; Black, L; Bryde, J	Pilot study of the safety and efficacy of Myobloc (botulinum toxin type B) for treatment of axillary hyperhidrosis	This study did not include HDSS as an outcome measure. The pivotal trial and economic model are structured around HDSS-defined health states. Without HDSS data, the effectiveness of GPB 1% cream could not be robustly compared using an ITC.
2021	Awaida, CJ; Rayess, YA; Jabbour, SF; Abouzeid, SM; Nasr, MW	Reduction of Injection Site Pain in the Treatment of Axillary Hyperhidrosis With Botulinum Toxin: A Randomized, Side-by-Side, Comparative Study of Two Injection Patterns	This study compared botulinum toxin injection techniques. To perform an ITC, the Company required studies that include a placebo arm.

Abbreviations: DLQI, Dermatology Life Quality Index; FMR, fractional microneedle radiofrequency; HDSS, Hyperhidrosis Disease Severity Scale; ITC, indirect treatment comparison; QoL, quality of life; SLR, systematic literature review; UK, United Kingdom.

Other trials

A26. The EAG noted another 1% GPB cream trial on review of the studies excluded from the review (NCT04159610). Please comment on the status of this trial and explain why it was not considered in this submission.

Response: This small study was not progressed. The original planned enrolment was 12 patients. No patients were enrolled for the study.

A27. Please provide a clinical study report for the Hyp-02/2015 Phase 1b dose-finding study, if one is available.

Response: The study report has been provided.

Marketing authorisation

A28. Priority question. The SmPC supplied for 1% GPB cream outlines the applicable population as those with severe forms of primary axillary hyperhidrosis. Please clarify how patients with severe forms of the condition are expected to be identified in UK clinical practice (i.e. which baseline measurements this is expected to be based on).

Response: Patients who do not achieve sufficient relief from first line therapy would be considered to have severe primary axillary hyperhidrosis. HDSS can also be used by primary care healthcare professionals to quickly assess severity.

Section B: Clarification on cost-effectiveness data

All updates to the economic model made in response to the Clarification Questions (CQs) are detailed within the relevant individual responses. Any CQ requiring a model update or scenario analysis has been implemented on a new sheet within the model titled "CQs," where a toggle function allows users to activate each specific scenario.

Following the CQs, the Company has revised its base case in response to the following questions:

- CQ B9 - the cost of non-axillary sweating/HH has been corrected
- CQ B12 – the cost of propantheline bromide has been updated to £20.74
- CQ B21 – the hardcoded values from the calculation of subsequent therapies has been removed

Table 76 presents the stepwise changes from the original Company base case to the revised base case for GPB 1% cream vs. antimuscarinics, and vs. botulinum toxin. These changes reflect a 9.4% reduction in the net monetary benefit (NMB) at a willingness-to-pay (WTP) threshold of £20,000 for GPB 1% cream vs. antimuscarinics and a 2.8% reduction in the NMB for GPB 1% cream vs. botulinum toxin. Each scenario is presented in comparison to the ***revised*** Company base case. The revised base case and corresponding revised sensitivity analyses are presented in Section D.

Table 76: Step changes from original Company base case to revised Company base case

	Vs. Antimuscarinics		Vs. Botulinum toxin	
	ICER	**NMB**	**ICER**	**NMB**
Original Company base case	Dominant	[redacted]	Dominant	[redacted]
Correction from CQ B9	Dominant	[redacted]	Dominant	[redacted]
Updated propantheline bromide cost from CQ B12	Dominant	[redacted]	Dominant	[redacted]
Removed hard coded values from subsequent therapies	Dominant	[redacted]	Dominant	[redacted]

	Vs. Antimuscarinics		Vs. Botulinum toxin	
	ICER	NMB	ICER	NMB
Revised Company base case	Dominant	[redacted]	Dominant	[redacted]

Abbreviations: CQ, clarification question; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit

Economic model context

B1. Priority question: In Figure 2 of the company submission (CS), the proposed position of glycopyronnium bromide (GPB) 1% cream is:

- **As an alternative to oral anticholinergic medication (anti-muscarinics) in primary care.**
- **Prior to oral anticholinergic medication (anti-muscarinics) and botulinum toxin type A (BTX) in secondary care.**

However, the economic model does not make a distinction between healthcare settings, instead implementing proportions of the type of care setting used for administration and monitoring of patients on GPB 1% cream and the comparators (Table 40 of the CS). Additionally, the company has assumed that GPB 1% cream is only administered in a primary care setting, which contradicts Figure 2 of the CS. The EAG considers that the company's approach means that the fully incremental analysis is uninterpretable.

To resolve these issues and provide interpretable results, the EAG strongly recommends developing two separate economic models for the cost-effectiveness analysis:

- **A primary care model:**
    - **Comparator: Oral antimuscarinics, specifically propantheline bromide. The EAG's clinical experts advised that propantheline bromide is the only licensed treatment for PAHH and would be predominantly prescribed by GPs (question B13);**

- **Subsequent treatments: please explore an assumption whereby lifetime QALYs for initial antimuscarinics, BTX and GPB 1% cream are used for the subsequent treatment health state (question B22).**

- **A secondary care model:**
  - **Comparators: Oral antimuscarinics, specifically modified-release oxybutynin 5mg once daily, per the EAG's clinical expert advice (question B14) and BTX.**
  - **Subsequent treatments: please explore an assumption whereby lifetime QALYs for initial antimuscarinics, BTX and GPB 1% cream are used for the subsequent treatment health state (question B22).**

Response: We acknowledge the potential confusion caused by Figure 2 in the CS, which indicates that GPB 1% cream may be used in both primary and secondary care settings, whereas the economic model assumes that 100% of GPB 1% cream use occurs in primary care. Although this distinction was not clearly presented, the model reflects the anticipated long-term use of the treatment. In the short term, some use in secondary care may occur, specifically for patients who were referred before GPB 1% cream became available. These patients may still receive the treatment via secondary care. However, over time, it is expected that patients will begin treatment in primary care, prior to any referral to secondary care, aligning with the assumptions in the model.

The feedback from the EAG's clinical experts is consistent with the positions outlined in Sections 3.2.3.2 and 3.5.1.2 of the CS regarding appropriate comparators for GPB 1% cream. It is anticipated that GPB 1% cream will eventually be used exclusively in the primary care setting. Clinical expert input provided to the Company also indicated that general practitioners (GPs) are generally reluctant to prescribe unlicensed treatments without guidance from secondary care.[13] Therefore, we agree with the EAG that propantheline bromide is likely to be the most relevant comparator to GPB 1% cream, and that both treatments are expected to be used in primary care in the long term. To reflect this, a scenario analysis has been conducted comparing GPB 1% cream with propantheline bromide alone. This scenario assumes 100% use of

propantheline bromide within the antimuscarinic comparator arm and 100% primary care administration for both GPB 1% cream and propantheline bromide. As 100% use of propantheline bromide is assumed, no A&G is included. This is because A&G is considered more relevant for unlicensed products, such as oxybutynin, when prescribed in the primary care setting. Table 77 shows that GPB 1% cream remains cost-effective based on a WTP of £20,000 in this scenario.

Table 77: Scenario analysis: 100% primary care administration for GPB 1% cream vs. 100% primary care administration for propantheline bromide | Clarification Question B1a

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Propantheline bromide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Note: applied to the revised Company base case.

As GPB 1% cream is not expected to be used in the secondary care setting long term, beyond its initial use in the existing prevalent secondary care population, a scenario assuming exclusive secondary care use of GPB 1% cream is considered less relevant to future clinical practice. However, in response to this specific question from the EAG, we have included an additional scenario comparing GPB 1% cream with oxybutynin 2.5mg (three times daily) and botulinum toxin, under the following assumptions 100% oxybutynin use within the weighted antimuscarinics comparator and 100% administration in secondary care for GPB 1% cream, oxybutynin, and botulinum toxin. This scenario is presented solely to address the EAG's request and does not reflect the expected long-term pattern of GPB 1% cream use, which is anticipated to occur exclusively in primary care. Table 78 shows that GPB 1% cream remains cost-effective based on a WTP of £20,000 in this scenario.

Table 78: Scenario analysis: 100% secondary care administration for GPB 1% cream vs. 100% secondary care administration for oxybutynin 2.5mg (three times daily) and 100% secondary care administration for botulinum toxin | Clarification Question B1b

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oxybutynin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

Time horizon

B2. Priority question: The EAG is concerned that the model's lifetime horizon may be excessive, given the nature of the condition and the treatments under consideration. Clinical experts advising the EAG indicate that treatment response typically becomes clear within the first month, allowing non-responders to quickly transition to alternative therapies. Furthermore, within two years, most patients are expected to have identified an effective treatment and are likely to remain on it long-term. In the study by Wade *et al.* (2017) hyperhidrosis was assumed to spontaneously resolve after the age of 65 years based on advice from clinical experts[4] and the EAG's own clinical experts said that they do not often see patients over the age of 50 years.

Consequently, a lifetime horizon may introduce unnecessary "noise" into the results, particularly because approximately 20 years of the model's estimates account for subsequent treatment costs without corresponding treatment benefits. This is based on the company's base-case assumption that patients return to a baseline HDSS score upon treatment discontinuation and initiation of subsequent therapy, which the EAG's clinical experts consider clinically implausible. Instead, a shorter time horizon may be appropriate to capture all

important differences in costs and outcomes between treatments and would still adhere to the NICE reference case. In the NICE manual, it states "*a time horizon shorter than a patient's lifetime could be justified if there is no differential mortality effect between technologies and the differences in costs and clinical outcomes relate to a relatively short period*". As such, please explore the following scenarios:

a) **A time horizon of 72 weeks, which reflects the observed period for Hyp-1 phase 3b.**

b) **A time horizon of two years, which reflects the EAG's clinical expert advice that this duration captures the most important differences in the clinical management of severe PAHH.**

When adjusting the time horizon, please ensure that the QALY shortfall analysis in tab "QALYShortfall" is updated to ensure that the severity modifier is not inappropriately applied.

Response: A lifetime time horizon was implemented in the base case following the scoping call with NICE on 27 February 2025, during which the NICE Technical Team advised that a lifetime horizon would be appropriate for a lifetime condition. Nevertheless, we acknowledge that a shorter time horizon may be informative in this context. To address this, two scenario analyses have been conducted:

1. Table 79 presents results using a 72-week time horizon, aligned with the duration of the Phase 3b clinical trial.
2. Table 80 presents results using a 2-year time horizon.

We confirm that the NICE severity modifier is not applied in either scenario. Both scenarios show that GPB 1% cream remains cost-effective based on a WTP of £20,000 when varying the time horizon in the model.

Table 79: Scenario analysis: 72-week time horizon | Clarification Question B2a

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

Table 80: Scenario analysis: 2-year time horizon | Clarification Question B2b

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

B3. Guidance in NICE DSU TSD 23 recommends using the ONS life tables from 2017-2019 due to the uncertainty about the long-term impact of COVID-19 on data beyond 2020. As such, please update the model to use the 2017-2019 ONS life tables.

Response: In the CS, mortality rates are taken from age- and gender-adjusted England and Wales lifetables 2021-23.[14] To explore the impact of COVID-19 on data beyond 20202, Table 81 presents the results using the ONS life tables from 2017-2019. GPB 1% cream remains cost-effective based on a WTP of £20,000 when using the ONS life tables from 2017-2019; this has a negligible impact on results with the NMB based on a WTP of £20,000 increasing by 0.03% and 0.04% in the comparison with antimuscarinics and botulinum toxin, respectively.

Table 81: Scenario analysis: background mortality from 2017-2019 | Clarification Question B3

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

Comparators

B4. Priority question: The EAG's clinical experts advised that BTX is one of the most effective treatments for severe PAHH and that patients would see a clinically significant reduction in sweating and improvement in quality of life within one week of treatment and this would be maintained up to month 4. The EAG's clinical experts consider that the company's base case assumption of treatment waning from week 4 for BTX was clinically implausible. As such, please provide a scenario where treatment waning for BTX is applied from month 4 to month 6 (administration of next injection).

Response: The onset of treatment effect waning for botulinum toxin in PAHH varies across studies. In the Company base case, the treatment effect is modelled with peak efficacy at 4 weeks, followed by a decline to no effect by 6 months, at which point patients are assumed to return to baseline HDSS values. In the CS, scenario analyses were presented assuming peak efficacy at 8 and 12 weeks. In response to the EAG's question, an additional scenario has been conducted assuming peak efficacy at 16 weeks (approximately 4 months). Table 82 presents the results of this scenario. GPB 1% cream remains cost-effective based on a WTP of £20,000 when assuming peak efficacy for botulinum toxin at 16 weeks; this has no impact on the comparison with antimuscarinics and reduces the NMB based on a WTP of £20,000 by 12.4% for the comparison with botulinum toxin.

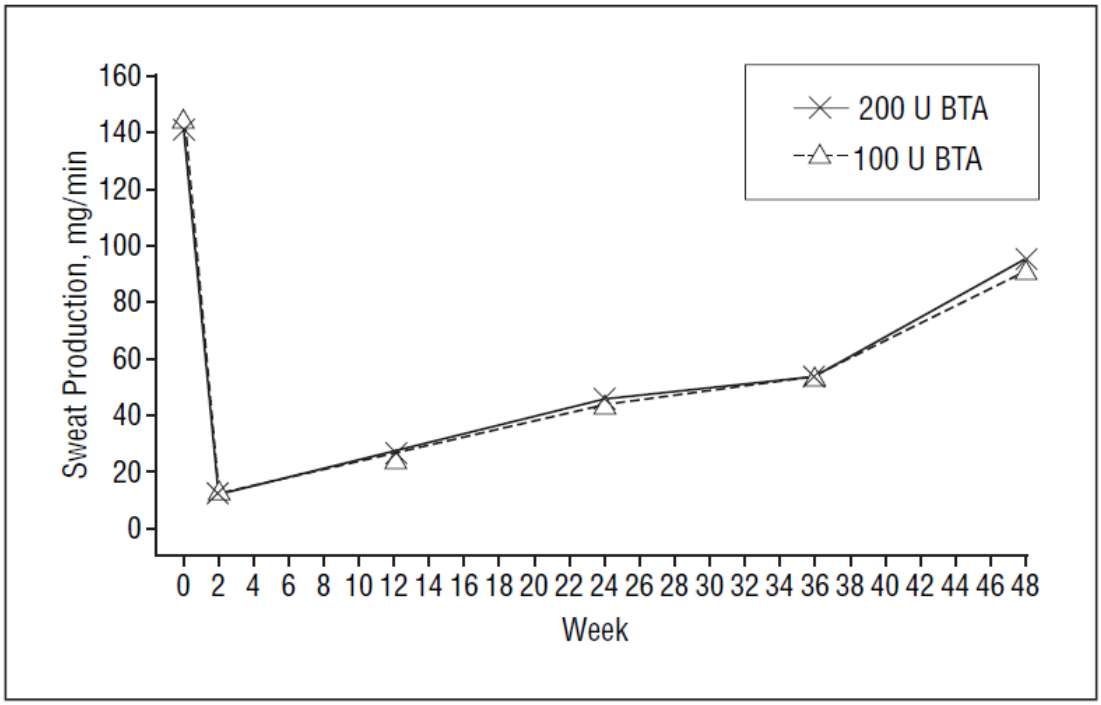
Table 82: Scenario analysis: peak efficacy for botulinum toxin at 16 weeks | Clarification Question B4

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

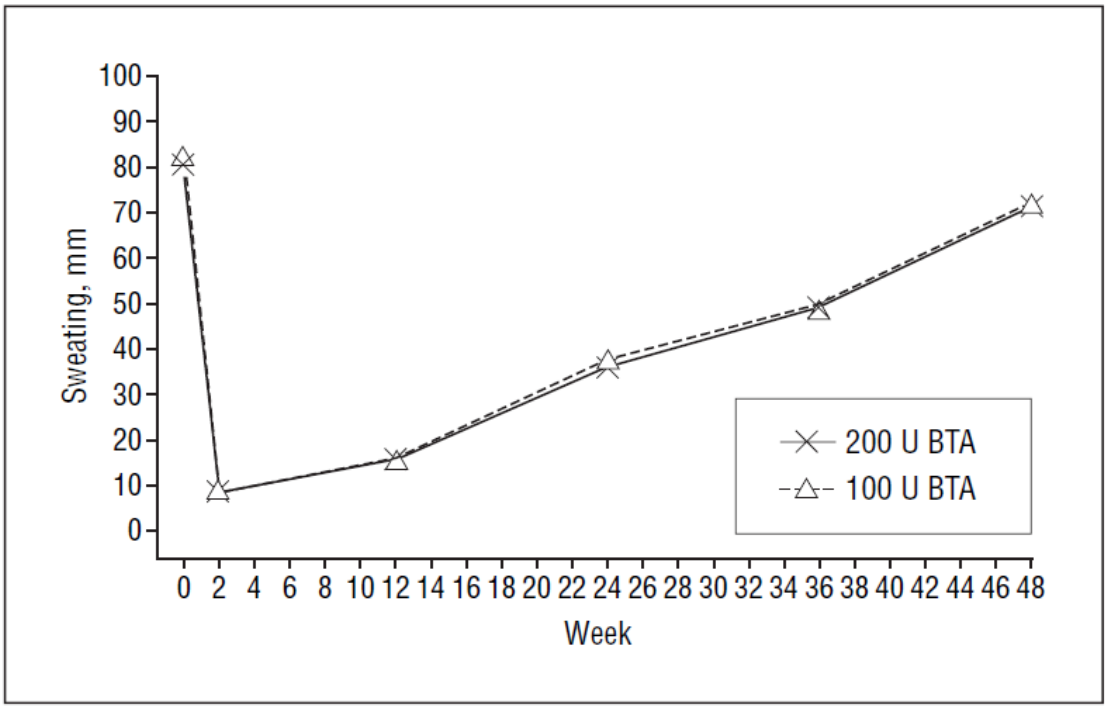
While this scenario is presented in response to the EAG's question, some literature suggests that peak efficacy at 4 weeks may be conservative. For example, Heckmann et al. (2005) investigated the efficacy of two doses of botulinum toxin in 43 patients with PAHH, using both gravimetric measurements of sweat production and patient self-assessments.[15] The results showed a significant reduction in sweat production by week 2 following treatment. However, from this point onward, a gradual waning of effect was observed. Figures (shown in Figure 3 and Figure 4) presented in the study illustrate the trend in sweat production and patient-reported sweating following the second treatment, clearly demonstrating that the treatment effect began to decline as early as week 2. Note: these data were only available for the second treatment cycle; similar data were not reported for the first treatment.

Figure 3: Comparison of sweat production after the second treatment with 200U or 100U of botulinum toxin | Heckmann et al. (2005)[15]



Abbreviations: BTA, botulinum toxin A

Figure 4: Comparison of sweating according to patients' rating after the second treatment with 200U or 100U of botulinum toxin | Heckmann et al. (2005)[15]



Abbreviations: BTA, botulinum toxin A

However, other data indicate that the peak efficacy may be between 4-16 weeks. For example, Naumann et al. (2001) reported a decline in efficacy between 4 and 16 weeks, Lee et al. (2022) indicated that peak efficacy might occur at 12 weeks, with a decline starting at 16 weeks, and Odderson et al. (2002) found that waning may commence around 4 months, though this study had a small sample size.[16–18]

B5. Please justify why using the proportional difference between ≥1 and ≥2 HDSS improvement ORs for antimuscarinics robustly estimates the data for ≥1 and ≥2 HDSS improvements for BTX. Please include evidence of the comparability of treatment effectiveness for BTX and antimuscarinics for improvement in HDSS score.

Response: In the absence of direct data reporting both ≥1-point and ≥2-point improvements in HDSS for botulinum toxin, we applied the proportional difference between these thresholds as observed in antimuscarinic data to estimate the corresponding outcome for botulinum toxin. This assumption does not imply that the overall treatment effect of botulinum toxin and antimuscarinics is comparable. Rather,

it assumes that the relationship between achieving a ≥1-point versus ≥2-point improvement in HDSS is consistent across treatments.

The two studies identified in the clinical SLR that reported HDSS outcomes for botulinum toxin (Lowe et al. (2007) and Lee et al. (2022)) only provided data for ≥2-point HDSS improvements, with no data available for the ≥1-point threshold.[8,17]

To assess the impact of this assumption, a scenario analysis was conducted (CS Section 3.10.3), in which the relative efficacy of GPB 1% cream versus botulinum toxin for ≥1-point HDSS improvement was assumed to be the same as that for ≥2-point improvement. This scenario has been re-run based on the revised Company base case (Section D) and the results indicate a 3.0% reduction in the NMB for GPB 1% cream compared with botulinum toxin, assuming a £20,000 WTP threshold. This highlights that the assumption is unlikely to influence the cost-effectiveness conclusions.

B6. Please provide instructions on how to run the combined BTX dose scenario (100U and 150U doses) and describe (with evidence) the assumptions underpinning the scenario.

a) The EAG's clinical experts considered that 80% of patients respond to the 100U dose of BTX and 20% will need a dose increase to 200U and switch to the Dysport® brand of BTX as its 300U pack is cheaper (£92.40) than other brands that have 200U packs in the BNF (cheapest is £259.80). As such, please run the combined BTX scenario where 80% of patients stay on the 100U dose of BTX and 20% switch to Dysport 300U for the second administration and beyond.

Response: On the "Efficacy" sheet of the model (row 76), there is a dropdown menu that allows the user to select the source of relative efficacy data for botulinum toxin compared with GPB 1% cream. In the Company's base case, data from Lowe et al. (2007) for the 100U dose of botulinum toxin are used, alongside the FASa data for GPB 1% cream.[8,19]

Selecting "Option 3" in the dropdown switches the botulinum toxin input to the combined 100U and 150U dose data from Lowe et al. (2007), while retaining the FASa

data for GPB 1% cream. This selection automatically updates the odds ratios used in the model for the ≥2-point HDSS improvement endpoint, as well as the adverse event (AE) rates. The combined dose data are derived by pooling patient numbers from both dose groups for response outcomes and by weighting adverse event data accordingly.

In response to the EAG's question, the model has been updated to allow for a different distribution of botulinum toxin formulations from the second administration onward. Table 83 presents the results of a scenario in which 100% of patients receive 100U of Botox at the first administration (as per the Company base case), and from the second administration onward, 80% continue 100U of Botox while 20% switch to 300U of Dysport. GPB 1% cream remains cost-effective based on a WTP of £20,000 in this scenario; this has a negligible impact on results with the NMB based on a WTP of £20,000 reducing by 0.02% and 0.06% in the comparison with antimuscarinics and botulinum toxin, respectively.

Table 83: Scenario analysis: 20% Dysport for patients receiving two or more botulinum toxin procedures | Clarification Question B6

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

Adverse events

B7. Priority question: The EAG's clinical experts advised that in clinical practice non-axillary sweating/hyperhidrosis is extremely rare with BTX. As such, please provide a scenario where the proportion of non-axillary sweating/ hyperhidrosis associated with BTX is removed.

Response: We do not agree that non-axillary sweating/HH is extremely rare with botulinum toxin; this contradicts the SmPC for Botox, NHS Information and Advice

leaflets for patients, and the evidence for botulin toxin from the literature. While botulinum toxin is administered locally and is not expected to cause systemic side effects, some patients do experience increased sweating at non-treated sites as part of a thermoregulatory response.

The SmPC for Botox 100 U classifies non-axillary sweating as a common occurrence in patients with PAHH.[20] Additionally, the NHS Information and Advice leaflets for patients highlight non-axillary sweating/HH as a risk.[21,22]

In the CS, the incidence of non-axillary sweating was based on data from Lowe et al. (2007), which also informed the efficacy estimates.[8] In this study, non-axillary sweating was reported in 6% of patients in the 100U botulinum toxin group and 10% in the 150U group, compared with 4% in the placebo group. The base case assumes 100U dosing, and therefore applies a 6% non-axillary sweating rate for botulinum toxin. This rate is consistent with other published evidence:

- **Lee et al. (2022)**: 4 patients (2.5%) in the botulinum toxin group reported compensatory sweating versus one patient in the placebo group.[17]
- **Naumann et al. (2001)**: 11 patients (5%) in the botulinum toxin group reported increased non-axillary sweating versus none in the placebo group.[23]
- **Odderson et al. (2002)**: 1 patient (5.6%) reported non-axillary compensatory HH versus none in the placebo group.[18]

Given the consistent reporting of low but non-zero rates of non-axillary sweating in the literature, and alignment with the clinical trial informing the model's efficacy inputs for botulinum toxin, we consider the base case assumption appropriate. However, to address the EAG's question, a scenario analysis assuming 0% incidence of non-axillary sweating with botulinum toxin has been conducted – see Table 84. GPB 1% cream remains cost-effective based on a WTP of £20,000 in this scenario; this has a negligible impact on results with the NMB based on a WTP of £20,000 reducing by 0.08% and 0.36% in the comparison with antimuscarinics and botulinum toxin, respectively.

Table 84: Scenario analysis: 0% non-axillary sweating for botulinum toxin | Clarification Question B7

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

B8. Priority question: The EAG's clinical experts advised that the adverse events (AEs) listed in Table 32 of the CS would generally not be severe enough to be treated and would likely be managed through dose reductions or treatment discontinuation (which is already captured in the model) within the first month of treatment. The EAG's clinical experts' view is aligned with the approach in Wade *et al*. (2017), which did not include AEs for medications or BTX. Additionally, in the clinical study report for Hyp1-18/2016, it is stated that [redacted] As such, please provide a scenario where the impact of AEs, for both costs and disutility, are excluded from the model.

Response: We do not agree that AEs should be excluded from the economic analysis. Treatments for PAHH are typically long-term due to the chronic nature of the condition, and tolerability is a key factor in determining patient experience and treatment adherence. While we acknowledge that most AEs associated with these treatments are mild or moderate and often managed via dose adjustment or discontinuation, they can still have a meaningful impact on patient HRQoL, which is a key goal in managing PAHH.

Except for the cost associated with non-axillary HH, the costs assigned to AEs in the model are minimal, either representing a GP consultation or 10 minutes of nurse

pharmacist time. These costs are considered appropriate, as it is reasonable to assume that patients experiencing AEs would seek professional advice prior to altering or stopping treatment.

The importance of AEs in treatment selection is also reflected in the SmPCs for antimuscarinics and highlighted in the NICE Evidence Summary on oxybutynin for hyperhidrosis.[24,25] This guidance recognises that while some patients may opt for oral treatments, many would prefer topical therapies due to the risk of systemic AEs associated with antimuscarinics.

Further, the Wade et al. (2017) publication, though it did not include costs or direct HRQoL impacts of AEs, acknowledges that oral anticholinergic doses required to control sweating can result in significant systemic AEs, such as drowsiness, dry mouth, blurred vision, constipation, confusion, and cardiac effects.[26] Wade et al. (2017) focused only on discontinuations due to AEs, which is an oversimplification. Their analysis does not account for dose titration strategies or the HRQoL burden associated with tolerating AEs, both of which are important considerations in real-world clinical management of PAHH.

Therefore, we consider the inclusion of AEs in the economic analysis clinically justified. A scenario that ignores known AE costs and HRQoL impact, particularly for antimuscarinics, does not reflect the realities of PAHH treatment decision-making and would not be a relevant scenario in this context.

B9. The cost of non-axillary sweating/hyperhidrosis is based on lifetime drug acquisition costs for antimuscarinics and a hardcoded value of 813.557506813909. Please explain the assumptions behind the estimation of the non-axillary sweating/hyperhidrosis cost in the model, including a description of the hardcoded data with underlying data and calculations to estimate the value.

Response: In the model and in Table 44 of Section 3.5.3 of the CS, the cost of non-axillary sweating/HH is assumed to align with the cost of antimuscarinic treatment in secondary care (i.e., drug acquisition plus administration). While the actual calculation pulls acquisition costs from the “Trace_AMSC” sheet, the administration cost was hardcoded to reflect 100% secondary care use of antimuscarinics, this is different to

the base case distribution for antimuscarinics of 25% primary care, 25% A&G, 50% secondary care. This was because non-axillary sweating/HH is only relevant to patients receiving botulinum toxin in the model, for whom treatment is in the secondary care setting.

However, we acknowledge that this hardcoding reduced model transparency and flexibility, and inadvertently introduced an error. The value used for the cost of non-axillary sweating/HH (£1,503.56) does not accurately reflect the intended administration costs for antimuscarinics. To correct this, we have now updated the model with administration cost components for antimuscarinics are broken down by setting within the "Trace_AMSC" sheet (columns AK:AN) and the non-axillary sweating/HH cost is now linked to these live values for both acquisition and administration.

The corrected cost of non-axillary sweating/HH in the model is £1,100.11. This correction leads to a minor impact on the cost-effectiveness results. This correction has been included within the revised Company base case and the impact on the results is shown in Table 76.

Health-related quality of life

B10. Priority question: The company has indicated that DLQI data are available from Hyp-1 phase 3a and 3b and that a mapping algorithm exists to convert these data to EQ-5D values.

a) **Please explore mapping pooled Hyp-1 3a and 3b DLQI data to EQ-5D and use appropriate methods to estimate utility values for HDSS1, HDSS2, HDSS3 and HDSS4. Please refer to the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 20 for methods and guidance on estimating, reporting and incorporating mapped utility values into cost-effectiveness analysis. Please fully report the methods used to**

obtain the final EQ-5D health state utilities and report the relevant data informing the estimates.

b) Please provide a scenario using the mapped EQ-5D health state utilities.

Response: As stated in Section 3.4.2 of the CS, although algorithms exist for mapping DLQI to EQ-5D, these have not been applied. The available algorithms were developed using data from broader dermatology populations (such as patients with psoriasis, atopic dermatitis, and other skin conditions) and may not adequately capture the specific burden and symptom profile experienced by individuals with PAHH.

Furthermore, as outlined in the response to the CQ submitted to NICE on 30th May 2025 and in response to CQ A23, Leith Healthcare does not have direct access to the IPD from the GPB 1% cream clinical trials. While there is a route to the IPD through the data holder, any access would require a formal request. Notably, no further analyses beyond those included in the CSR were requested by regulators. Therefore, only aggregate data are available from the Phase 3a and 3b clinical trials, limiting the ability to account for patient-level heterogeneity or adjust for relevant covariates. As a result, applying mapping algorithms could produce overly simplistic and potentially biased utility estimates.

Drug acquisition and administration costs

B11. The EAG considers the company's approach to the inclusion of a [redacted] % compliance rate and mean number of applications per week for GPB 1% cream from Hyp-1 phase 3b accounts for dose variation twice. For example, based on mean number of applications per week up to week 4 in Hyp-1 phase 3b (Table 24 of the CS), the mean grams used is [redacted] g ([redacted] x 2 + [redacted] x 2]*1.08 g). In Table 2 of the CS, the company describes that to administer a single dose of GPB 1%

cream patients are to, "*fully press the pump twice to apply the recommended amount of cream to the top of the cap*".

a) **Please explain the value of [redacted] that is used to estimate the mean grams used in the first 29 days of treatment ([redacted] g), that then informs the compliance rate for GPB 1% cream.**
    i) **Please clarify if the data used to estimate the compliance rate are from Hyp-1 phase 3a or phase 3b.**
b) **Please justify why the company's base case approach of including both compliance and mean number of applications per week is appropriate and does not underestimate the acquisition costs for GPB 1% cream.**
c) **Please explain the difference in mean grams used for the first 29 days based on the company's estimation in the CS ([redacted] g) and the EAG's estimation based on mean number of applications and recommended dose per application ([redacted] g).**
d) **Please provide a scenario where the compliance rate for GPB 1% cream is 100%.**

Response (a): The value of [redacted] represents the difference between the actual product use and the protocol-specified product use in the Phase 3b clinical trial, as reported in Table 5.4.3_b of the CSR, for patients up to and including Day 29 (Week 4).[19]

There is a typographical error in Section 3.2.3.1 of the CS: the difference between the expected dose (as per protocol: [redacted]_g) and the actual usage should equal [redacted]_g. However, this error is limited to the text and does not affect the underlying calculation or the model. The compliance rate of [redacted] % used in the analysis is correct.

Response (b): As described above, the compliance rate reflects the difference between actual product use and the protocol-specified use over the first 4 weeks of treatment, based on dispenser returns. Compliance was assessed by weighing returned dispensers and comparing the amount used to the expected usage per protocol over 29 days.

This compliance measure does not capture the number of applications but rather the quantity of product used. For reference, the average number of applications in Weeks 2 and 4 was [redacted] and [redacted] respectively - closely aligned with the daily application recommended in the protocol.

The observed difference in compliance reflects that some patients applied a lower dose per application than recommended, not that they missed applications. In other words, compliance captures the proportion of the intended dose used by patients who applied the treatment, while application frequency reflects how often the product was used without accounting for dose size.

While there may be some conceptual overlap between these inputs, the near-daily application rate in the first 4 weeks suggests that the difference in product usage is primarily due to lower per-application dosing, not reduced application frequency.

Therefore, we believe it is appropriate to apply the compliance estimate from the first 4 weeks, when application frequency was consistent with the protocol, and to use application frequency from the long-term follow-up period for the remainder of the model.

Response (c): As described above, there is a typographical error in Section 3.2.3.1 of the CS: the difference between the expected dose (as per protocol: [redacted] g) and the actual usage should equal [redacted] g ([redacted] - [redacted]). However, this error is limited to the text and does not affect the underlying calculation or the model. The compliance rate of [redacted] % used in the analysis is correct. It is unclear where the EAG's number of [redacted] g has come from.

Response (d): In response to the EAG's request, Table 85 presents a scenario analysis assuming 100% compliance with GPB 1% cream. Note: this indirectly also assumed 100% compliance for unlicensed GPB as compliance is assumed the same across these therapies. However, as outlined above, we believe this scenario does not reflect the variability in dosing that would occur in clinical practice among patients using GPB 1% cream. GPB 1% cream remains cost-effective based on a WTP of £20,000 when assuming 100% compliance; this reduces the NMB based on a WTP of

£20,000 by 6.7% for the comparison with antimuscarinics and increases the NMB by 3.6% for the comparison with botulinum toxin.

Table 85: Scenario analysis: 100% compliance with GPB 1% cream | Clarification Question B11

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

B12. Priority question: In the latest edition of the BNF (April 2025), the drug tariff price for propantheline bromide is £20.74. NICE recommends that the lowest price available for medicines is used for cost-effectiveness analysis. Please update the model to use the cost of £20.74 for propantheline bromide.

Response: As discussed in Section 3.5.1 of the CS, prices for propantheline bromide on the BNF range from £20.74 to £195.14. Due to recent supply shortages of the lower-cost formulation, higher-cost packs have been more commonly used in UK clinical practice. Accordingly, the higher cost of £103.52 was used in the original Company base case to reflect UK clinical practice, with a scenario analysis assessing the impact of the lower £20.74 cost, presented in Section 3.10.3 of the CS.[47]

However, from the most recent primary care data in England (March 2025) the price of propantheline bromide has returned to £20.74. Therefore, the cost of £20.74 for propantheline bromide has been included within the revised Company base case and the impact on the results is shown in Table 76.

B13. Priority question: The EAG's clinical experts advised that in primary care, propantheline bromide would be prescribed to patients as it is the only licensed treatment for PAHH and would be predominantly prescribed by GPs. Please provide a scenario where the drug acquisition costs of oral

muscarinics in the primary care model is only based on propantheline bromide. Please ensure the lowest price available for propantheline bromide is used (£20.74).

Response: In the response to Clarification Question B1a a scenario analysis is provided comparing GPB 1% cream with propantheline bromide alone. This scenario assumes 100% use of propantheline bromide within the antimuscarinic comparator arm and 100% primary care administration for both GPB 1% cream and propantheline bromide. This scenario is based on the revised Company base case which includes the £20.74 pack cost for propantheline bromide, as per the response to CQ B12.

B14. Priority question: The EAG's clinical experts advised that in secondary care, modified-release oxybutynin 5 mg once daily would be prescribed to patients. Please provide a scenario where the drug acquisition cost of oral muscarinics in the secondary care model is only based on modified-release oxybutynin 5 mg once daily.

Response: As detailed in the response to CQ B1b, GPB 1% cream is not expected to be used in the secondary care setting long term, beyond its initial use in the existing prevalent secondary care population. Therefore, a scenario assuming exclusive secondary care use of GPB 1% cream is considered less relevant to future clinical practice.

However, in response to CQ B1b, a scenario analysis is provided comparing GPB 1% cream with oxybutynin 2.5mg (three times daily) and botulinum toxin, under the following assumptions 100% oxybutynin use within the weighted antimuscarinics comparator and 100% administration in secondary care for GPB 1% cream, oxybutynin, and botulinum toxin. In response to the EAG's question for this CQ, an additional scenario is presented which compares GPB 1% cream with modified-release oxybutynin 5 mg once daily, under the following assumptions 100% oxybutynin use within the weighted antimuscarinics comparator and 100% administration in secondary care for GPB 1% cream and oxybutynin. The cost of modified-release oxybutynin 5 mg is £28.16 for 28 tablets, as sourced from the BNF June 2025.[27] These scenarios are presented solely to address the EAG's requests and do not reflect the expected long-term pattern of GPB 1% cream use, which is anticipated to occur

exclusively in primary care. Table **86** shows that GPB 1% cream remains cost-effective based on a WTP of £20,000 in this scenario.

Table 86: Scenario analysis: 100% secondary care administration for GPB 1% cream vs. modified-release oxybutynin 5 mg once daily | Clarification Question B14

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oxybutynin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

B15. Priority question: The EAG's clinical experts advised that use of advice and guidance (A&G) services by GPs would only happen once to support diagnosis and treatment of a patient and that ongoing support would not be provided. Additionally, the EAG's clinical experts advised that very few hyperhidrosis patients are seen through A&G services. Thus, it is likely approximately 10% of GPs would use A&G services to diagnose and treat patients with severe PAHH.

As such, please conduct a scenario where the additional cost of A&G services is only applied to the first appointment for 10% of primary care patients in the antimuscarinics arm of the primary care model.

Response: As described in Section 3.5.1.2 in the CS, our clinical expert feedback suggests that GPs in England are being encouraged to use Advice & Guidance (A&G) services with hospital specialists to help reduce elective care referrals. As this is a relatively new initiative, the extent of its uptake remains uncertain.

While we agree that A&G is unlikely to be used for initiating frontline therapy, we note that GPB 1% cream is positioned for patients with severe PAHH who have not responded adequately to first-line treatment. We believe A&G is likely to be more

relevant for these patients, particularly in cases where GPs are prescribing unlicensed products in primary care.

In the base case, it is assumed that 50% of antimuscarinic prescriptions are managed in primary care. Of these, half are assumed to proceed without A&G input, and the other half with A&G input. In response to the EAG's question, an alternative scenario is presented, where 45% of all patients are assumed not to have A&G and 5% are assumed to have A&G (i.e., 10% of those in the primary care setting). Additionally, as per the EAG request, A&G costs are only applied to the initial appointment. Table **87** shows the results of the scenario. GPB 1% cream remains cost-effective based on a WTP of £20,000 in this scenario; this has a negligible impact on results with the NMB based on a WTP of £20,000 reducing by 0.3% and no impact in the comparison with antimuscarinics and botulinum toxin, respectively.

Table 87: Scenario analysis: 5% A&G administration for antimuscarinics in the first administration only | Clarification Question B15

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

B16. In the calculation of administration monitoring costs for BTX, BTX procedure costs are multiplied by the unadjusted HDSS health states (tab "Trace_BTX, columns O:R) and secondary care unit costs are multiplied by the half cycle corrected HDSS health states (tab "Trace_BTX, columns W:Z). Please justify the approach in the model.

Response: The Company base case assumes that the botulinum toxin procedure is administered at the start of the relevant cycle. As a result, no half-cycle correction was applied to drug acquisition and procedure costs. However, for administration monitoring costs, it was assumed that appointments could occur at any point during the cycle (consistent with the assumptions for GPB 1% cream and antimuscarinics) so a half-cycle correction was applied.

The Company acknowledges the EAG clinical experts' feedback (CQ B19) indicating that patients receiving botulinum toxin are typically monitored during their scheduled treatment appointment. Therefore, a scenario analysis has been conducted using non–half-cycle-adjusted monitoring appointments for botulinum toxin.

Table **88** presents the results of this scenario. GPB 1% cream remains cost-effective based on a WTP of £20,000 in this scenario; this has a negligible impact on results with the NMB based on a WTP of £20,000 with no impact and an increase of 0.2% in the comparison with antimuscarinics and botulinum toxin, respectively

Table 88: Scenario analysis: Non-half-cycle-adjusted monitoring appointments for botulinum toxin | Clarification Question B16

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

B17. Priority question: In the company's base case, two costs are applied for the administration of BTX, one based on the NHS reference costs HRG code JC42A and the other cost is based on 45 minutes of band 5 nurse time. The EAG understands that the company's approach is based on that used in Wade *et al*. (2017). However, the EAG considers the approach and rationale in Wade *et al*. (2017) is not clear. Additionally, the EAG's clinical experts advised that the appointment to review a patient and deliver treatment would be 20 minutes.

a) **Please clarify what the NHS reference cost includes and justify, beyond its use in Wade *et al.* (2017), why it is appropriate to include in the model in conjunction with the nurse delivery cost and acquisition cost of BTX.**

b) **Please conduct a scenario analysis that only uses the cost of 20 minutes of band 5 nurse time for the administration cost of BTX.**

Response: In the base case, the cost of administering botulinum toxin was aligned with the approach used by Wade et al. (2017).[26] Specifically, the unit cost was based on the NHS reference cost associated with Healthcare Resource Group (HRG) code JC42A (Intermediate Skin Procedures (aged ≥13 years, General Surgery category)), along with the cost of 45 minutes of Band 5 nurse time.[28,29] Wade et al. (2017) noted that this approach was advised by UK clinical experts, and as such, it was considered appropriate for this appraisal.

In response to the EAG's question, the Company has conducted further investigation and cannot find a HRG code explicitly designated for botulinum toxin administration. However, under the HRG4+ 2025/26 Local Payment Grouper, localised HH maps to HRG code JD07, which includes a range of skin disorders with and without interventions.[30] When averaging day-case appointments across JD07 codes (JD07A to JD07K), the cost is approximately £535. Notably, this includes both interventional and non-interventional cases. When limiting the analysis to JD07 codes with interventions, the weighted average day-case cost increases substantially to £1,601. The day-case setting reflects publicly available NHS protocols for the administration of botulinum toxin.[21,31–33]

In comparison, the cost used in the base case (based on the assumptions from Wade et al. (2017)) include £156 for HRG JC42A plus £35.25 for 45 minutes of Band 5 nurse time, totalling £191.25. This suggests that the cost of administering botulinum toxin in a day-case setting in the base case may be significantly underestimated.

To address this, a scenario analysis has been conducted using the £535 cost, representing the weighted average of day-case appointments across the JD07 HRG codes. This scenario excludes additional nurse time costs. However, it should be noted that even this may be a conservative estimate, as it includes cases without interventions. Table **89** presents the results of this scenario. There is no impact on the results for GPB 1% cream vs. antimuscarinics. However, the NMB based on a WTP threshold of £20,000 has increased by 22.2% for GPB 1% cream vs. botulinum toxin. GPB 1% cream remains cost-effective in this scenario.

Table 89: Scenario analysis: Cost of £535 for the administration of botulinum toxin | Clarification Question B17

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

The scenario requested by the EAG, which assumes only the cost of 20 minutes of Band 5 nurse time for the administration of botulinum toxin, is not considered appropriate. Botulinum toxin administration is a specialist procedure typically carried out in dedicated clinics, requiring specific infrastructure and clinical oversight. Even if the injection itself were to take 20 minutes, which is inconsistent with feedback from clinical experts in the Wade et al. (2017) publication and published NHS protocols, this estimate fails to capture the broader resource use involved, including clinic setup, equipment, support staff, and post-procedure observation. These costs are not

reflected in nurse time alone and are more accurately represented by relevant HRG-based costs.

Patient monitoring

B18. Priority question: The EAG's clinical experts advised that patients on oral antimuscarinics, and likely for GPB 1% cream, will be monitored annually in primary care, regardless of whether treatment was prescribed in secondary care. Additionally, the EAG's clinical experts explained that BTX patients would be monitored as part of their next scheduled treatment appointment. This would be conducted by the administering nurse, rather than with a consultant, and the appointment (including administering treatment) would take 20 minutes. The EAG's clinical expert view is aligned with the assumption included in Wade *et al*. (2017), which assumed no follow-up visits for patients on BTX. Therefore, please provide a scenario where:

- **Monitoring of patients on GPB 1% cream and oral antimuscarinics for both primary and secondary care, is annual and the cost is based on a primary care appointment.**
- **The cost of monitoring for BTX is excluded.**
- **The cost of patient review and delivery of BTX is based on 20 minutes of a band 5 nurse time (question B17b).**

Response: Table **90** presents the results of a scenario in which initial appointments for patients receiving GPB 1% cream or antimuscarinics are allocated according to the assumed distribution of care settings i.e., 100% in primary care for GPB 1% cream, and for antimuscarinics, 25% in primary care, 25% in primary care with A&G, and 50% in secondary care. For all subsequent administration and monitoring appointments, the setting is assumed to be primary care (without A&G). In this scenario, monitoring costs for botulinum toxin are excluded. GPB 1% cream remains cost-effective based on a WTP of £20,000 in this scenario; the NMB reduces based on a WTP of £20,000 by 2.9% for the comparison with antimuscarinics and by 12.0% for the comparison with botulinum toxin.

Note: as described in the response to CQ B17, the scenario requested by the EAG, which assumes only the cost of 20 minutes of Band 5 nurse time for the administration of botulinum toxin, is not considered appropriate. Botulinum toxin administration is a specialist procedure typically carried out in dedicated clinics, requiring specific infrastructure and clinical oversight. Even if the injection itself were to take 20 minutes, which is inconsistent with feedback from clinical experts in the Wade et al. (2017) publication and published NHS protocols, this estimate fails to capture the broader resource use involved, including clinic setup, equipment, support staff, and post-procedure observation. These costs are not reflected in nurse time alone and are more accurately represented by relevant HRG-based costs. Therefore, this component is not included within the scenarios.

Table 90: Scenario analysis: Primary care monitoring assumed for GPB 1% cream and antimuscarinics and no monitoring costs for botulinum toxin | Clarification Question B18

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

Treatment discontinuation

B19. Priority question: The EAG's clinical experts considered that most treatment discontinuations for antimuscarinics occur in the first month of treatment and that around 1/3rd of patients discontinue treatment. After the first month, the remaining patients are assumed to have a good response to treatment and that the overall discontinuation rate over time is around 10%. Assuming a time horizon of 2 years, the EAG calculates that the 2-week

instantaneous rate of discontinuation is 0.20% for oral antimuscarinics after week 4.

a) **Please conduct a scenario where 33.3% of patients on oral antimuscarinics discontinue treatment at week 4 (no discontinuations prior to that) and thereafter the 2-weekly rate of discontinuation is 0.20%.**
b) **Please combine the scenario in part a) with the two-year time horizon scenario from question B2b.**

Response (a): As outlined in Section 3.3.3.2 of the CS, the base case treatment duration for antimuscarinics is informed by Wolosker et al. (2014).[34] This study was a randomised controlled trial involving 431 patients with AHH, aligned with the target population for this appraisal. By 6 months, 188 patients (50.9%) had discontinued treatment.

A scenario analysis presented in Section 3.10.3 of the CS uses an alternative data source (Millán-Cayetano et al. (2017)), a retrospective review of 110 patients with hyperhidrosis treated with oxybutynin.[35] This study reported a 35% discontinuation rate at 12 months. However, the broader HH population makes it less relevant than Wolosker et al. (2014).

Feedback from the EAG's clinical experts suggests a discontinuation rate of approximately 43%, with 33% of patients stopping treatment in the first month and a further 10% discontinuing over an unspecified period. While this estimate is broadly consistent with published literature, the time period of discontinuation is unclear. The EAG have proposed using a two-year time horizon to derive an instantaneous discontinuation rate of 0.20% per cycle – it is unclear where this time period has come from.

Nevertheless, in response to the EAG's request, a scenario analysis is presented assuming that one-third of patients treated with antimuscarinics discontinue gradually over the first four weeks (rather than all at once, which was considered clinically implausible), followed by a per-cycle discontinuation rate of 0.20%. Table **91** presents the results of this scenario. Note: this scenario predicts high costs for the

antimuscarinics comparator driven by the one-off subsequent therapy costs which are accrued by a large proportion of patients early in the model time horizon (reducing the level of discounting). GPB 1% cream remains cost-effective based on a WTP of £20,000.

Table 91: Scenario analysis: Treatment duration for antimuscarinics informed by EAG clinical experts | Clarification Question B19a

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

Response (b): Table **92** presents the results of this scenario assuming a 2-year time horizon i.e., aligned with the response to CQ B2b. GPB 1% cream remains cost-effective based on a WTP of £20,000 in this scenario; the NMB increases based on a WTP of £20,000 by 316.1% for the comparison with antimuscarinics and reduces by 38.4% for the comparison with botulinum toxin.

Table 92: Scenario analysis: Treatment duration for antimuscarinics informed by EAG clinical experts and a 2 year time horizon | Clarification Question B19b

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

B20. Priority question: The EAG's clinical experts considered that a monthly discontinuation rate for BTX is not reflective of current practice. They considered that after the first treatment, patients would be booked in for their second treatment and then response to treatment assessed at that appointment (after 6 months). At the second injection appointment, the dose would be adjusted based on response. As such, discontinuation of treatment is only likely to happen at the third treatment if patients aren't responding to BTX. Therefore, the EAG considers it is more appropriate to apply treatment discontinuation in the model at the timepoint of each BTX treatment in the model (every 6 months), and this aligns with the data presented in Table 31 of the CS.

Please provide a scenario where treatment discontinuation for BTX is applied according to the treatment schedule (aligned with Table 31). Please ensure that the data on discontinuation of treatment (and therefore initiation of subsequent treatment) from Table 31 is only used for the scenario.

The EAG acknowledges that in the Lowe *et al*. (2007) study, a proportion of patients completed treatment and received no further injections after 1, 2 and 3 injections. However, the EAG considers data on study completion from Lowe *et al.* (2007), should not inform treatment discontinuation as the trial design was such that based on monitoring during the trial, patients were only eligible for retreatment if they had a HDSS score of 3 or 4 and at least 50 mg of spontaneous resting axillary sweat over 5 minutes in each axilla. Therefore, the EAG understands that patients who completed the study were those that were not eligible for retreatment due to maintained response to previous treatment.

Additionally, the Lowe *et al*. study is from 2007 and may not reflect the current clinical practice. The EAG's clinical experts advised that if patients have a good response to BTX, most receive their next scheduled injections and can remain on treatment for many years.

Response: In response to the EAG's request, an option has been incorporated into the model to apply discontinuation rates for botulinum toxin at the point of each

administration. Based on data from Lowe et al. (2007), as presented in Table 31 of the CS, this approach results in the following discontinuation rates:

- 31.5% discontinue after the first administration (i.e., prior to the second administration),
- 50.0% discontinue after the second administration (i.e., prior to the third),
- For subsequent administrations, a constant discontinuation rate is applied, based on the average of the first two time points.

These rates are derived using the base case assumption that all patients who formally discontinued treatment, along with half of those who completed the study without seeking further treatment, are considered true discontinuers. It should be noted that data for the third and fourth administrations from Lowe et al. (2007) were not included in the model due to the small sample sizes and limited follow-up beyond the second treatment.

Table **93** presents the results using this approach. As expected, the impact on the base case results is minimal. This is because the overall proportion of patients who discontinue remains the same; only the timing of discontinuation is adjusted. GPB 1% cream remains cost-effective based on a WTP of £20,000 in this scenario; the NMB reduces based on a WTP of £20,000 by 0.1% for the comparison with antimuscarinics and by 1.9% for the comparison with botulinum toxin.

Table 93: Scenario analysis: Updated approach to modelling discontinuation with botulinum toxin | Clarification Question B20a

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Note: applied to the revised Company base case.

Table **94** shows the impact of only including patients who had formally discontinued treatment reported in the Lowe et al. (2007) publication with the updated approach described above. GPB 1% cream remains cost-effective based on a WTP of £20,000 in this scenario; the NMB increases based on a WTP of £20,000 by 1.2% for the comparison with antimuscarinics and reduces by 13.7% for the comparison with botulinum toxin.

Table 94: Scenario analysis: Updated approach to modelling discontinuation with botulinum toxin and assuming only formal discontinuations from Lowe et al. (2007) | Clarification Question B20b

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

Subsequent treatments

B21. Priority question: In the economic model, the calculation of subsequent treatment costs is not transparent. For example, the formula to estimate the cost of antimuscarinics (secondary care) in tab "Costs", cell D64, has a link to lifetime drug acquisition costs (Trace_AMSC!$AF$3), lifetime adverse event costs (Trace_AMSC!$AH$3) and a hardcoded value of 383.112809909026, which has not been described in the CS - as such, the EAG cannot validate this. Please provide a description and the underlying calculations to obtain the following values in the model and ensure this is included in the model.

Tab	Cell reference	Value	Description and underlying values (and any required calculations)

Costs	D62	102.619502654203	
Costs	D63	148.228170500516	
Costs	D64	383.112809909026	
Costs	D65	1177.83436060385	
Costs	D66	1130.90836450528	

Response: As outlined in Table 41 of Section 3.5.2 of the CS, the model assumes that the cost of subsequent therapies is equal to the sum of acquisition, monitoring, and AE costs associated with the relevant initial therapy.

While the acquisition and AE costs were already drawn dynamically from the "Trace" sheets, the administration costs were previously hardcoded to reflect the appropriate treatment setting. We acknowledge that this approach reduced transparency and flexibility within the model.

To improve clarity and consistency, the model has been updated so that administration costs are now also sourced directly from the relevant "Trace" sheets. Specifically, the formulae in cells D62:D66 on the "Costs" sheet have been revised to eliminate hardcoded values. This update leads to a minor impact on the cost-effectiveness results, with differences only appearing beyond the 11th decimal place. This update has been included within the revised Company base case and the impact on the results is shown in Table 76

B22. Priority question: The EAG considers that the company's approach to the modelling of subsequent treatments is fundamentally flawed as patients accrue subsequent treatment costs in the model, but return to their baseline HDSS score, resulting in costs and benefits that are not aligned. Additionally, the company references that their assumption is aligned with that in Bloudek *et al*. (2021), but the EAG considers this is incorrect, as the paper states that "*upon discontinuation with no subsequent treatment, patients reverted to baseline HDSS scores for the remainder of the modeled time horizon*".[5] Furthermore, in the Bloudek *et al*. (2021) response rates for subsequent

therapies and associated benefits are included in the cost-effectiveness analysis.

The company's base case approach is biased against the comparators as the company's model estimates that most patients move to subsequent treatment after [redacted] months for antimuscarinics and [redacted] years for BTX and then spend approximately [redacted] years accruing costs and no benefits of subsequent treatment. Patients on for GPB 1% cream move to subsequent treatment after [redacted] years and spend approximately [redacted] years on subsequent treatment.

a) **Please provide a justification for why lifetime drug acquisition, administration, monitoring and AE costs for initial antimuscarinics, BTX and GPB 1% cream have been used for subsequent treatments, but the modelled benefits of these treatments have not been excluded in the model?**

b) **Please provide a scenario where the lifetime QALYs for initial antimuscarinics, BTX and GPB 1% cream are used for the subsequent treatment health state.**

    i) **Please combine this scenario with the time horizon scenarios requested in question B2b and the treatment discontinuation scenarios requested in question B19 and B20.**

Response (a): Firstly, to clarify that the model applies a one-off cost for subsequent therapy, which reflects the drug acquisition, administration, monitoring, and AE costs associated with the initial therapy. This approach assumes that the costs of treatment for follow-up therapies are broadly comparable to those of the initial treatment. In the base case, the mean duration of treatment with the initial therapies is [redacted] years for GPB 1% cream, 0.7 years for antimuscarinics, and 1.3 years for botulinum toxin. Therefore, the drug acquisition, administration, monitoring, and AE costs are not lifetime costs, nor are they incurred over a patient's full lifetime. Rather, the cost is applied once, at the point of discontinuation of the initial therapy.

Given that the average age of patients entering the model is [redacted] years and that PAHH is not associated with increased mortality, it is reasonable to assume that patients

discontinuing initial treatment could receive subsequent therapy for a duration of up to [redacted] years.

Secondly, regarding the HRQoL benefit associated with subsequent therapies, the base case assumes that patients requiring further treatment revert to their baseline HDSS score. This assumption reflects the clinical pathway in which patients have not only failed to respond adequately to first-line therapy but have also discontinued a second-line option. At this stage, it is anticipated that their underlying PAHH may be more difficult to manage, and therefore, they are unlikely to experience the same level of benefit as those who respond earlier in the treatment pathway. Nevertheless, patients are still expected to incur the full costs associated with subsequent therapies.

Response (b): As outlined in the response to CQ B22a, lifetime costs are not applied to patients receiving subsequent therapies. Consequently, it would not be appropriate to apply lifetime QALYs for these patients. A more formal approach, such as explicitly modelling subsequent therapies using a payoff method, was considered. However, this was deemed overly complex given the limited data available in this setting.

Instead, a pragmatic approach has been taken, in which patients are assumed to revert to the average HDSS health states observed during treatment with their respective initial therapies. Utility values are then applied based on these health states. While this scenario is presented to explore uncertainty around the assumed HRQoL benefit and HDSS response by line of therapy, it should be noted that this is a conservative assumption, as it applies the same level of benefit to patients regardless of whether they are receiving first-line or subsequent therapy. It also assumes that patients maintain the HDSS response from subsequent therapy for the duration of the model time horizon.

Table **95** presents the impact of this scenario over a two-year time horizon (CQ B2b). A two-year horizon is used because the model assumes lifetime benefits from subsequent therapies, which is unrealistic given that patients typically do not remain on these treatments for life. As such, a two-year time frame provides a more appropriate basis for interpreting the scenario. GPB 1% cream remains cost-effective based on a WTP of £20,000 in this scenario. However, the incremental QALYs become very small in both comparisons (less than [redacted]). Therefore, a cost-comparison

approach may be more appropriate for interpretation; GPB 1% cream is shown to cost £[redacted] less than the antimuscarinics arm and £[redacted] less than the botulinum toxin arm.

Table 95: Scenario analysis: Assuming the same HDSS response as observed for initial therapies for subsequent therapies and a 2 year time horizon | Clarification Question B22b

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

Response (bi): Table **96** presents the results of the scenario assuming the same HDSS response as observed for initial therapies for subsequent therapies (CQ B22b), a 2 year time horizon (CQ B2b), treatment discontinuation for antimuscarinics informed by EAG clinical experts (CQ B19), and an updated approach to modelling discontinuation with botulinum toxin and assuming only formal discontinuations from Lowe et al. (2007) (CQ B20). Note: As highlighted in the response to CQ B22b, this scenario assumes the same level of benefit for patients regardless of their line of therapy. This is likely a conservative assumption. GPB 1% cream remains cost-effective based on a WTP of £20,000 in this scenario; the NMB based on a WTP of £20,000 increases by 436.6% when GPB 1% cream is compared with antimuscarinics and reduces by 58.8% when compared with botulinum toxin.

Table 96: Scenario analysis: Assuming the same HDSS response as observed for initial therapies for subsequent therapies, a 2 year time horizon, treatment discontinuation for antimuscarinics informed by EAG clinical experts and an updated approach to modelling discontinuation with botulinum toxin and assuming only formal discontinuation from Lowe et al. (2007) | Clarification Question B22bi

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

B23. Priority question: The EAG considers there is a lack of clarity around the inclusion of unlicensed GPB 2% cream for subsequent treatments.

a) **Please explain (with evidence) why patients who have discontinued treatment with GPB 1% cream would not be given GPB 2% cream.**
b) **Please provide evidence for the treatment effectiveness of unlicensed GPB 2% cream compared with GPB 1% cream?**
    i) **Based on the evidence provided, please provide a scenario that incorporates the effectiveness of GPB 2 % cream in terms of total QALYs associated with subsequent treatment, as requested in question B22b.**

Response (a): GPB creams of different concentrations have been used in the UK as unlicensed medicines for the treatment of cranio-facial and axillary hyperhidrosis. From the March England SCMD hospital data,[36] the following GPB cream products were used

- Glycopyrronium bromide 2% in Cetomacrogol cream (Formula A)
- Glycopyrronium bromide 1% in Cetomacrogol cream (Formula A)
- Glycopyrronium bromide 2% in Generic Unguentum M cream
- Glycopyrronium bromide 0.5% in Generic Unguentum M cream

- Glycopyrronium bromide 2% in Cetomacrogol cream (Formula A)
- Glycopyrronium bromide 0.5% in Cetomacrogol cream (Formula A)
- Glycopyrronium bromide 2% in Cetomacrogol cream (Formula A)
- Glycopyrronium bromide 4% in Cetomacrogol cream (Formula A)

The most used concentration is 2%, most likely as this is the strength listed on the BAD guidance for unlicensed products as an option for cranio-facial hyperhidrosis. As these products are unlicensed and manufactured locally or by special order manufacturers, they have not been subject to clinical studies, there is no guarantee of consistency of supplied product and there is no data on the relationship between the concentration of product and the local absorption achieved. Prior to the availability of licensed GPB 1% cream, there has been no option for a licensed treatment in the UK. In accordance with MHRA guidance[37], HCPs are expected to use a licensed treatment when one is available, hence our expectation that use of unlicensed cream will reduce and eventually largely cease as GPB 1% cream is made available. If a patient discontinues GPB 1% cream due to lack of efficacy, there is no evidence to suggest that increasing the concentration would lead to a clinical benefit. Similarly, if discontinuation is due to tolerability issues, a higher concentration would likely exacerbate these AEs. Therefore, it would not be appropriate to offer GPB cream at higher concentrations to patients who have discontinued GPB 1% cream, either due to lack of effect or poor tolerability. Whatever the reason for discontinuation, the prescribing clinician would seek an alternative treatment with a different mechanism of action, rather than escalating the dose of the same agent.

B24. The EAG's clinical experts validated Table 43 of the CS and considered that the company's assumption of subsequent treatments did not reflect

current clinical practice. Instead, they provided an alternative view of subsequent treatments, outlined in the table below. Please provide a scenario using the proportions in the table below and combine with the scenario requested in question B2b. Additionally, for patients who go on to have no further treatment, the EAG's clinical experts advised that 1/3rd of these seek privately funded treatments. As such, for the scenario, please assume that of the patients who have no further NHS treatment, 1/3rd remain in their final HDSS health state (patients do not return to baseline HDSS scores) and the remainder return to baseline HDSS scores.

	Proportion of subsequent therapies after initial:		
	GPB 1% cream	Antimuscarinics	Botulinum toxin
Antimuscarinics (primary care)	0.0%	0.0%	0.0%
Antimuscarinics (primary care and A&G)	0.0%	0.0%	0.0%
Antimuscarinics (secondary care)	10.0%	10.0%	25.0%
Botulinum toxin (secondary care)	80.0%	63.0%	0.0%
Unlicensed GPB (secondary care)	0.0%	2.0%	25.0%
No further NHS treatment/ patients discharged from care (secondary care model only)	10.0%	25.0%	50.0%

Response: In response to the EAG's request, two additional subsequent therapy options ("no further treatment" and "private treatment") have been incorporated into the economic model within the "Costs" sheet. A scenario analysis reflecting the EAG's advised distribution of subsequent therapies is presented in Table **98**, with the assumed proportions detailed in Table 97.

For patients receiving "no further treatment", it is assumed they revert to their baseline HDSS distribution, reflecting a return to untreated disease severity. For those receiving "private treatment", patients are assumed to experience a benefit equivalent to the average HDSS health state achieved during their initial therapy. For example, if a

patient initially received GPB 1% cream and subsequently receives private treatment, their HDSS health state is assumed to reflect the average observed during GPB 1% cream use. This approach is consistent with the methodology used for other subsequent therapy scenarios, as described in the response to CQ B22.

GPB 1% cream remains cost-effective based on a WTP of £20,000 in this scenario; the NMB based on a WTP of £20,000 reduces by 94.9% when GPB 1% cream is compared with antimuscarinics and by 93.0% when compared with botulinum toxin.

Table 97: Subsequent therapy distribution | Clarification Question B24

	Proportion of subsequent therapies after initial:		
	GPB 1% cream	Antimuscarinics	Botulinum toxin
Antimuscarinics (primary care)	0.0%	0.0%	0.0%
Antimuscarinics (primary care and A&G)	0.0%	0.0%	0.0%
Antimuscarinics (secondary care)	10.0%	10.0%	25.0%
Botulinum toxin (secondary care)	80.0%	63.0%	0.0%
Unlicensed GPB (secondary care)	0.0%	2.0%	25.0%
Private treatment	3.3%	8.3%	16.7%
No further treatment	6.7%	16.7%	33.3%

Table 98: Scenario analysis: Assuming subsequent therapy distribution based on EAG's clinical feedback and assuming the same HDSS response as observed for initial therapies for subsequent therapies | Clarification Question B24a

Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£/QALY)**	**NMB (WTP £20,000)**
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Note: applied to the revised Company base case.

Table **99** presents the results of the scenario assuming the subsequent therapy distribution based on EAG's clinical feedback (CQ B24), assuming the same HDSS response as observed for initial therapies for subsequent therapies (CQ B22), and a 2 year time horizon (CQ B2b). GPB 1% cream remains cost-effective based on a WTP of £20,000 in this scenario; the NMB based on a WTP of £20,000 reduces by 74.7% when GPB 1% cream is compared with antimuscarinics and by 68.8% when compared with botulinum toxin.

Table 99: Scenario analysis: Assuming subsequent therapy distribution based on EAG's clinical feedback, assuming the same HDSS response as observed for initial therapies for subsequent therapies, and a 2 year time horizon | Clarification Question B24b

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

B25. Priority question: The company has used lifetime costs for GPB 1% cream (with an estimated multiplier) to estimate subsequent treatment costs associated with GPB 2% cream, which also includes the [redacted] % compliance rate as well as the mean number of applications per week in Hyp-1 phase 3b. The EAG considers that the company's approach discounts the subsequent cost of GPB three times, once for initial compliance with GPB 1% cream,

another when using mean application per two weeks and then a third time for assumed compliance with unlicensed GPB 2% cream.

a) **Please provide evidence for the [redacted] % assumed compliance rate for unlicensed GPB 2% cream.**

b) **Please explain how the company base case approach is appropriate and does not underestimate costs for subsequent GPB 2% cream.**

c) **Please provide a scenario where compliance for both GPB 1% cream and GPB 2% cream is 100%. In this scenario, the mean number of applications per week from Hyp-1 phase 3b accounts for dose variation.**

Response (a, b): As outlined in the response to CQ B23, although GPB 1% and GPB 2% creams differ in concentration, they are formulations of the same active substance, glycopyrronium bromide. Therefore, the economic model assumes the inputs underpinning the GPB 1% and 2% cream costs are identical.

Response (c): In response to CQ B11d, a scenario analysis was provided in which compliance for GPB 1% cream was set to 100%. As the model assumes the same compliance for both GPB 1% and GPB 2% creams, this scenario in Table **85** effectively reflects 100% compliance for both formulations.

As outlined in the response to CQ B11, the mean number of applications per week does not reflect dose variation among users. Compliance refers to the proportion of the intended dose actually used by patients who apply the treatment, whereas application frequency indicates how often the product is applied, without accounting for the amount used per application.

Section C: Textual clarification and additional points

C1. Priority question: Please provide a convergence plot for the probabilistic sensitivity analysis (PSA) and ensure this is included in the economic model.

Response: A convergence plot has been incorporated into the "PSA" sheet of the economic model, featuring a dropdown menu that allows users to toggle between the comparisons (GPB 1% cream vs. antimuscarinics or vs. botulinum toxin) and outcome measures (ICER or NMB). While the ICER convergence plots show some variability across both comparisons, the NMB plots demonstrate convergence after approximately 200 iterations for both the antimuscarinic and botulinum toxin comparisons.

The probabilistic ICERs are observed to be unstable, primarily due to the small magnitude of the incremental QALYs, which occasionally cross zero. As a result, the ICER can fluctuate between positive and negative values or become extremely large, leading to an erratic convergence pattern. Additionally, some PSA simulations produce dominated (more costly and less effective) or dominant (less costly and more effective) results, scenarios in which the ICER is difficult to interpret. In contrast, the NMB remains more stable and interpretable across all simulations.

The convergence plots are presented for the revised Company probabilistic scenarios in Section D.

C2. The disutility for non-axillary hyperhidrosis in the CS (-0.12182) does not match the model (-0.12457). Please clarify which value is correct and make the appropriate amendment in the model, if necessary.

Response: The value reported in Table 34 of the CS contains a typographical error. The correct disutility applied in the model for non-axillary HH is –0.12457, which is based on the average utility decrement from HDSS score 1 to scores 2, 3, and 4.

C3. The EAG could not validate the proportions presented in Table 25 of the CS against the source, which was stated to be Wade *et al*. (2017) Please clarify the page number in Wade *et al*. (2017), where the data were extracted from.

Response: The proportions presented in Table 25 of the CS reflect the data presented in Table 64 from Wade et al. (2017).[26] These reflect the number of respondents reporting use of oxybutynin (n=30), propantheline bromide (n=23), and oral glycopyrrolate (n=12).

Section D: Revised Company base case

Table 76 presents the stepwise changes from the original Company base case to the revised base case for GPB 1% cream vs. antimuscarinics, and vs. botulinum toxin. These changes reflect a 9.4% reduction in the NMB at a WTP threshold of £20,000 for GPB 1% cream vs. antimuscarinics and a 2.8% reduction in the NMB for GPB 1% cream vs. botulinum toxin. The revised base case and corresponding revised sensitivity analyses are presented below.

Revised base-case results

Table 77 presents the revised base case pairwise results vs. GPB 1% cream and Table 101 presents the revised incremental analysis.

Table 102 presents the corresponding revised net health benefits (NHBs) vs. GPB 1% cream.

GPB 1% cream vs. antimuscarinics

In the revised base case analysis, GPB 1% cream generates [redacted] additional QALYs at a reduced cost of [redacted] compared to antimuscarinics. As it delivers greater health benefits at a lower overall cost, GPB 1% cream is considered dominant relative to antimuscarinics. The additional QALYs are primarily driven by patients remaining on GPB 1% cream for a longer duration, maintaining HDSS response over time. Furthermore, the utility decrement associated with AEs is lower for GPB 1% cream than for antimuscarinics. Although the acquisition and administration costs of GPB 1% cream are higher, these are offset by savings from fewer AEs and a reduced need for subsequent therapies, due to sustained treatment. The NHB is [redacted] at a WTP threshold of £20,000, and [redacted] at a threshold of £30,000. Corresponding NMBs are [redacted] and [redacted], respectively.

GPB 1% cream vs. botulinum toxin

In the base case analysis, GPB 1% cream generates [redacted] additional QALYs at a reduced cost of [redacted] compared to botulinum toxin. As it delivers greater health benefits at a lower overall cost, GPB 1% cream is considered dominant relative to botulinum toxin. The additional QALYs are primarily driven by patients remaining on GPB 1% cream for a longer duration, maintaining HDSS response over time. Furthermore, the utility decrement associated with AEs is lower for GPB 1% cream than for botulinum toxin. Cost savings are demonstrated for GPB 1% cream across administration, AEs, and subsequent therapies compared to botulinum toxin. The NHB is [redacted] at a WTP threshold of £20,000, and [redacted] at a threshold of £30,000. Corresponding NMBs are [redacted] and [redacted], respectively.

Table 100: Revised base-case results vs. GPB 1% cream

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 101: Revised incremental analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 102: Revised net health benefit vs. GPB 1% cream

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

Revised sensitivity analyses

Probabilistic sensitivity analysis

The proportion of PSA iterations where GPB 1% cream is considered cost-effective is [redacted] at a £20,000/QALY threshold. The CEAC is shown in Figure 5.

The convergence plots for the PSA for vs. antimuscarinics and vs. botulinum toxin are presented in

Figure 6 and Figure 7, respectively, based on the NMB endpoint. As detailed in the response to CQ C1 the NMB plots demonstrate convergence after approximately 200 iterations for both the antimuscarinic and botulinum toxin comparisons. The probabilistic ICERs are observed to be unstable, primarily due to the small magnitude of the incremental QALYs, which occasionally cross zero. As a result, the ICER can fluctuate between positive and negative values or become extremely large, leading to an erratic convergence pattern. Additionally, some PSA simulations produce dominated (more costly and less effective) or dominant (less costly and more effective) results, scenarios in which the ICER is difficult to interpret. In contrast, the NMB remains more stable and interpretable across all simulations.

Figure 5: Revised CEAC

Abbreviations: CEAC, cost-effectiveness acceptability curve; GPB, glycopyrronium bromide.

Figure 6: PSA convergence plot for GPB 1% cream vs. antimuscarinics

Abbreviations: GPB, glycopyrronium bromide; NMB, net monetary benefit; PSA, probabilistic sensitivity analysis

Figure 7: PSA convergence plot for GPB 1% cream vs. botulinum toxin

Abbreviations: GPB, glycopyrronium bromide; NMB, net monetary benefit; PSA, probabilistic sensitivity analysis

GPB 1% cream vs. antimuscarinics

The PSA results indicate an average incremental cost of [redacted] and an average incremental QALY gain of [redacted] for GPB 1% cream compared to antimuscarinics. These results are consistent with the deterministic analysis, confirming that GPB 1%

cream is dominant (i.e., more effective and less costly). This consistency is visually supported by the overlap of the deterministic and probabilistic base case markers in the cost-effectiveness plane (Figure 8).

Figure 8: Revised cost-effectiveness plane (1,000 iterations) | GPB 1% cream vs. antimuscarinics

Abbreviations: GPB, glycopyrronium bromide; QALY, quality adjusted life year; WTP, willingness-to-pay.

GPB 1% cream vs. botulinum toxin

For the comparison with botulinum toxin, the PSA shows an average incremental cost of [redacted] and an average incremental QALY gain of [redacted] for GPB 1% cream. Again, the probabilistic results are aligned with the deterministic findings, indicating dominance of GPB 1% cream. This is further evidenced by the overlap in the deterministic and probabilistic results on the cost-effectiveness plane (Figure 9).

Figure 9: Revised cost-effectiveness plane (1,000 iterations) | GPB 1% cream vs. botulinum toxin

Abbreviations: GPB, glycopyrronium bromide; QALY, quality adjusted life year; WTP, willingness-to-pay.

Deterministic sensitivity analysis

GPB 1% cream vs. antimuscarinics

Results for the ten most influential parameters for GPB 1% cream vs. antimuscarinics are shown in Table **103** and depicted in a tornado diagram in Figure **10** and Figure 11 based on the ICER and a NMB with a WTP of £20,000, respectively.

As in the original Company base case, across all parameter variations within their respective lower and upper bounds, GPB 1% cream remains dominant compared to antimuscarinics, except in two scenarios: when the upper bound of the utility value for the HDSS=4 health state and the lower bound for the HDSS=2 health state are applied.

In these scenarios, GPB 1% cream appears less effective and less costly than antimuscarinics, placing the ICER in the south-west quadrant of the cost-effectiveness plane. However, these results should be interpreted with caution. For example, setting the HDSS=2 utility value to the lower bound ([redacted]) produces a utility that is lower than those of the more severe HDSS=3 and HDSS=4 health states, which is not clinically plausible. As more severe health states are expected to correspond with lower

HRQoL, this contradicts clinical expectations. Additionally, the confidence intervals for these utility values were derived from published literature and are associated with large standard deviations. As a result, the sensitivity analyses incorporate wide parameter ranges.

Table 103: Top ten parameters impacting the ICER (revised one-way sensitivity analysis) | GPB 1% cream vs. antimuscarinics

Parameter	Lower bound	Upper bound	Difference
Antimuscarinics: 2-week proportion of AEs, Non-axillary sweating/hyperhidrosis	[redacted]	[redacted]	[redacted]
Antimuscarinics: proportion Unlicensed GPB (secondary care)	[redacted]	[redacted]	[redacted]
Utilities HDSS=4	[redacted]	[redacted]	[redacted]
Antimuscarinics: Proportion of discontinuations 0-26 weeks	[redacted]	[redacted]	[redacted]
Antimuscarinics: proportion Botulinum toxin (secondary care) subsequent therapy	[redacted]	[redacted]	[redacted]
GPB 1% cream: Proportion of discontinuations 0-72 weeks	[redacted]	[redacted]	[redacted]
GPB 1% cream: proportion Botulinum toxin (secondary care) subsequent therapy	[redacted]	[redacted]	[redacted]
Utilities HDSS=3	[redacted]	[redacted]	[redacted]
Antimuscarinics: 2-week proportion of AEs, Dry mouth	[redacted]	[redacted]	[redacted]
Antimuscarinics: proportion antimuscarinics (secondary care) subsequent therapy	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; ICER, incremental cost-effectiveness ratio.

Figure 10: Tornado plot, ICER (revised one-way sensitivity analysis) | GPB 1% cream vs. antimuscarinics

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; ICER, incremental cost-effectiveness ratio.

Figure 11: Tornado plot, NMB at a WTP of £20,000 (revised one-way sensitivity analysis) | GPB 1% cream vs. antimuscarinics

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; NMB, net monetary benefit; WTP, willingness-to-pay.

GPB 1% cream vs. botulinum toxin

Results for the ten most influential parameters for GPB 1% cream vs. botulinum toxin are shown in Table 104 and depicted in a tornado diagram in Figure 12 and Figure 13 based on the ICER and a NMB with a WTP of £20,000, respectively.

As in the original Company base case, across all parameter variations within their respective lower and upper bounds, GPB 1% cream remains dominant compared to botulinum toxin, except in two scenarios: when the upper bound of the utility value for the HDSS=4 health state and the lower bound for the HDSS=2 health state are applied. The same parameters influencing the interpretation of results in the comparison between GPB 1% cream and antimuscarinics also apply to the comparison with botulinum toxin, and the same caveats remain relevant.

Table 104: Top ten parameters impacting the ICER (revised one-way sensitivity analysis) | GPB 1% cream vs. botulinum toxin

Parameter	Lower bound	Upper bound	Difference
Utilities HDSS=4	[redacted]	[redacted]	[redacted]
Utilities HDSS=3	[redacted]	[redacted]	[redacted]
Utilities HDSS=2	[redacted]	[redacted]	[redacted]
Subsequent therapy costs: unlicensed GPB (secondary care)	[redacted]	[redacted]	[redacted]
Botulinum toxin: proportion unlicensed GPB (secondary care) subsequent therapy	[redacted]	[redacted]	[redacted]
Botulinum toxin: Proportion of discontinuations 0-26 weeks	[redacted]	[redacted]	[redacted]
Unlicensed GPB: cost per tube	[redacted]	[redacted]	[redacted]
Subsequent therapy costs: Botulinum toxin (secondary care)	[redacted]	[redacted]	[redacted]
Utilities HDSS=1	[redacted]	[redacted]	[redacted]
Number of Botulinum toxin procedures per year	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; ICER, incremental cost-effectiveness ratio.

Figure 12: Tornado plot, ICER (revised one-way sensitivity analysis) | GPB 1% cream vs. botulinum toxin

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; ICER, incremental cost-effectiveness ratio.

Figure 13: Tornado plot, NMB at a WTP of £20,000 (revised one-way sensitivity analysis) | GPB 1% cream vs. botulinum toxin

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; NMB, net monetary benefit; WTP, willingness-to-pay.

Scenario analysis

Scenario analyses were conducted to assess structural uncertainty within the economic model. The corresponding results from the deterministic analyses for GPB 1% cream vs. antimuscarinics are shown in Table 105 and Table 106 for the ICER and NMB with a WTP of £20,000, respectively. For GPB 1% cream vs. botulinum toxin these are shown in Table 107 and Table 108, respectively.

Across all scenarios, GPB 1% cream remains cost-effective i.e., the NMB remains positive at a WTP threshold of £20,000. Probabilistic scenario analyses were not conducted for the revised Company base case, as the results from the original base case showed strong alignment between probabilistic and deterministic analyses. Furthermore, the revisions to the base case are relatively minor.

GPB 1% cream vs. antimuscarinics

Table 105: Revised deterministic scenario analyses (ICER) | GPB 1% cream vs. antimuscarinics

Scenario name	ICER	% change from base case
Base case	[redacted]	NA
Time horizon: 4-years	[redacted]	2080.5%
Time horizon: 5-years	[redacted]	1322.6%
Time horizon: 10-years	[redacted]	230.3%
Half cycle correction: excluded	[redacted]	34.8%
Discount rate: 0% costs and 0% outcomes	[redacted]	-370.8%
Baseline characteristics: FASa	[redacted]	3.7%
Baseline characteristics: PPSb	[redacted]	1.7%
Baseline GPB 1% cream efficacy: PPSb	[redacted]	-23.2%
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	-22.8%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on PPSa	[redacted]	-1.1%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on Wade et al. (2017)	[redacted]	-0.9%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on PPSa	[redacted]	0.0%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on Wade et al. (2017)	[redacted]	0.0%
Relative efficacy of GPB 1% cream vs. botulinum toxin ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	0.0%
Dose of botulinum toxin assumed 150U	[redacted]	11.5%
Dose of botulinum toxin assumed combined of 100U and 150U	[redacted]	5.7%
Relative efficacy for 2+ botulinum toxin procedures based on Lowe et al. (2007)	[redacted]	0.0%

Scenario name	ICER	% change from base case
Relative efficacy for 2+ botulinum toxin procedures based on a 10% reduction in OR	[redacted]	0.0%
Relative efficacy for 2+ botulinum toxin procedures based on a 20% reduction in OR	[redacted]	0.0%
Maximum botulinum toxin efficacy achieved at week 8	[redacted]	0.0%
Maximum botulinum toxin efficacy achieved at week 12	[redacted]	0.0%
1.8 botulinum procedures per year	[redacted]	0.9%
Cost of propantheline bromide of £20.74	[redacted]	0.0%
Dose per day of oxybutynin of 12.5mg	[redacted]	6.3%
Dose intensity for oral antimuscarinics assumed equal to GPB 1% cream	[redacted]	-155.7%
Increase in discontinuation rate with GPB 1% cream of 10%	[redacted]	220.9%
Increase in discontinuation rate with GPB 1% cream of 20%	[redacted]	440.1%
Source of discontinuation for antimuscarinics from Millan-Cayetano et al. (2017)	[redacted]	23003.5%
Discontinuation for botulinum toxin assumed as only those who were formally discontinued	[redacted]	65.9%
Discontinuation for botulinum toxin assumed as those who were formally discontinued and no further treatment	[redacted]	-12.9%

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; GPB, glycopyrronium bromide; NMB, net monetary benefit; PPS, per-protocol set; WTP, willingness-to-pay.

Table 106: Revised deterministic scenario analyses (NMB based on a £20,000 WTP) | GPB 1% cream vs. antimuscarinics

Scenario name	NMB	% change from base case
Base case	[redacted]	NA
Time horizon: 4-years	[redacted]	-21.1%
Time horizon: 5-years	[redacted]	-15.8%
Time horizon: 10-years	[redacted]	-3.8%
Half cycle correction: excluded	[redacted]	0.7%
Discount rate: 0% costs and 0% outcomes	[redacted]	7.6%
Baseline characteristics: FASa	[redacted]	-0.9%
Baseline characteristics: PPSb	[redacted]	-0.4%
Baseline GPB 1% cream efficacy: PPSb	[redacted]	29.6%
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	29.0%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on PPSa	[redacted]	1.1%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on Wade et al. (2017)	[redacted]	0.9%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on PPSa	[redacted]	0.0%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on Wade et al. (2017)	[redacted]	0.0%
Relative efficacy of GPB 1% cream vs. botulinum toxin ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	0.0%
Dose of botulinum toxin assumed 150U	[redacted]	0.2%
Dose of botulinum toxin assumed combined of 100U and 150U	[redacted]	0.1%
Relative efficacy for 2+ botulinum toxin procedures based on Lowe et al. (2007)	[redacted]	0.0%
Relative efficacy for 2+ botulinum toxin procedures based on a 10% reduction in OR	[redacted]	0.0%

Scenario name	NMB	% change from base case
Relative efficacy for 2+ botulinum toxin procedures based on a 20% reduction in OR	[redacted]	0.0%
Maximum botulinum toxin efficacy achieved at week 8	[redacted]	0.0%
Maximum botulinum toxin efficacy achieved at week 12	[redacted]	0.0%
1.8 botulinum procedures per year	[redacted]	0.0%
Cost of propantheline bromide of £20.74	[redacted]	0.0%
Dose per day of oxybutynin of 12.5mg	[redacted]	0.1%
Dose intensity for oral antimuscarinics assumed equal to GPB 1% cream	[redacted]	-3.0%
Increase in discontinuation rate with GPB 1% cream of 10%	[redacted]	-3.7%
Increase in discontinuation rate with GPB 1% cream of 20%	[redacted]	-6.8%
Source of discontinuation for antimuscarinics from Millan-Cayetano et al. (2017)	[redacted]	-33.7%
Discontinuation for botulinum toxin assumed as only those who were formally discontinued	[redacted]	1.3%
Discontinuation for botulinum toxin assumed as those who were formally discontinued and no further treatment	[redacted]	-0.3%

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; GPB, glycopyrronium bromide; NMB, net monetary benefit; PPS, per-protocol set; WTP, willingness-to-pay.

GPB 1% cream vs. botulinum toxin

Table 107: Revised deterministic scenario analyses (ICER) | GPB 1% cream vs. botulinum toxin

Scenario name	ICER	% change from base case
Base case	[redacted]	NA
Time horizon: 20-years	[redacted]	88.7%
Time horizon: 40-years	[redacted]	59.8%
Time horizon: 60-years	[redacted]	10.5%
Half cycle correction: excluded	[redacted]	1.2%
Discount rate: 0% costs and 0% outcomes	[redacted]	-23.4%
Baseline characteristics: FASa	[redacted]	1.0%
Baseline characteristics: PPSb	[redacted]	0.4%
Baseline GPB 1% cream efficacy: PPSb	[redacted]	-31.6%
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	-22.0%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on PPSa	[redacted]	1.4%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on Wade et al. (2017)	[redacted]	4.6%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on PPSa	[redacted]	-2.6%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on Wade et al. (2017)	[redacted]	0.3%
Relative efficacy of GPB 1% cream vs. botulinum toxin ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	4.6%
Dose of botulinum toxin assumed 150U	[redacted]	1.8%
Dose of botulinum toxin assumed combined of 100U and 150U	[redacted]	0.9%
Relative efficacy for 2+ botulinum toxin procedures based on Lowe et al. (2007)	[redacted]	4.6%
Relative efficacy for 2+ botulinum toxin procedures based on a 10% reduction in OR	[redacted]	-0.8%

Scenario name	ICER	% change from base case
Relative efficacy for 2+ botulinum toxin procedures based on a 20% reduction in OR	[redacted]	-1.8%
Maximum botulinum toxin efficacy achieved at week 8	[redacted]	8.5%
Maximum botulinum toxin efficacy achieved at week 12	[redacted]	15.3%
1.8 botulinum procedures per year	[redacted]	4.8%
Cost of propantheline bromide of £20.74	[redacted]	0.0%
Dose per day of oxybutynin of 12.5mg	[redacted]	0.1%
Dose intensity for oral antimuscarinics assumed equal to GPB 1% cream	[redacted]	-2.6%
Increase in discontinuation rate with GPB 1% cream of 10%	[redacted]	11.2%
Increase in discontinuation rate with GPB 1% cream of 20%	[redacted]	22.3%
Source of discontinuation for antimuscarinics from Millan-Cayetano et al. (2017)	[redacted]	43.6%
Discontinuation for botulinum toxin assumed as only those who were formally discontinued	[redacted]	421.3%
Discontinuation for botulinum toxin assumed as those who were formally discontinued and no further treatment	[redacted]	-37.0%

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; GPB, glycopyrronium bromide; NMB, net monetary benefit; PPS, per-protocol set; WTP, willingness-to-pay.

Table 108: Revised deterministic scenario analyses (NMB based on a £20,000 WTP) | GPB 1% cream vs. botulinum toxin

Scenario name	NMB	% change from base case
Base case	[redacted]	NA
Time horizon: 20-years	[redacted]	-24.1%
Time horizon: 40-years	[redacted]	-18.0%
Time horizon: 60-years	[redacted]	-4.5%
Half cycle correction: excluded	[redacted]	0.3%
Discount rate: 0% costs and 0% outcomes	[redacted]	6.2%
Baseline characteristics: FASa	[redacted]	-0.7%
Baseline characteristics: PPSb	[redacted]	-0.3%
Baseline GPB 1% cream efficacy: PPSb	[redacted]	31.6%
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	19.3%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on PPSa	[redacted]	-1.0%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on Wade et al. (2017)	[redacted]	-3.0%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on PPSa	[redacted]	1.9%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on Wade et al. (2017)	[redacted]	-0.2%
Relative efficacy of GPB 1% cream vs. botulinum toxin ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	-3.0%
Dose of botulinum toxin assumed 150U	[redacted]	1.0%
Dose of botulinum toxin assumed combined of 100U and 150U	[redacted]	0.5%
Relative efficacy for 2+ botulinum toxin procedures based on Lowe et al. (2007)	[redacted]	-3.0%
Relative efficacy for 2+ botulinum toxin procedures based on a 10% reduction in OR	[redacted]	0.6%

Relative efficacy for 2+ botulinum toxin procedures based on a 20% reduction in OR	[redacted]	1.2%
Maximum botulinum toxin efficacy achieved at week 8	[redacted]	-5.3%
Maximum botulinum toxin efficacy achieved at week 12	[redacted]	-9.1%
1.8 botulinum procedures per year	[redacted]	-1.5%
Cost of propantheline bromide of £20.74	[redacted]	0.0%
Dose per day of oxybutynin of 12.5mg	[redacted]	0.0%
Dose intensity for oral antimuscarinics assumed equal to GPB 1% cream	[redacted]	-0.8%
Increase in discontinuation rate with GPB 1% cream of 10%	[redacted]	-4.0%
Increase in discontinuation rate with GPB 1% cream of 20%	[redacted]	-7.4%
Source of discontinuation for antimuscarinics from Millan-Cayetano et al. (2017)	[redacted]	13.7%
Discontinuation for botulinum toxin assumed as only those who were formally discontinued	[redacted]	-12.7%
Discontinuation for botulinum toxin assumed as those who were formally discontinued and no further treatment	[redacted]	0.9%

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; GPB, glycopyrronium bromide; NMB, net monetary benefit; PPS, per-protocol set; WTP, willingness-to-pay.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Glycopyrronium bromide cream (Axhidrox®) for treating severe primary axillary hyperhidrosis [ID6487]

Follow-up Clarification questions

July 2025

File name	Version	Contains confidential information	Date
ID6487_GPB 1% cream_PAHH_Response to EAG follow-up clarification questions 020725 [redacted]	v1.0	No	4 July 2025

Notes for company

Highlighting in the template

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Section A: Clarification on position of GPB 1% cream in the treatment pathway

A29. Priority question: Throughout the company's clarification response, it was stated several times that the company's proposed position of GPB 1% cream in the treatment pathway is as 2nd line treatment in primary care, as an alternative to oral anticholinergics. However, the company also stated that there would be a small prevalent population in secondary care that would be given GPB 1% cream as an alternative to oral anticholinergics prior to consideration for treatment with botulinum toxin A (BTX) treatment. However, the company's revised base case model still assumes 100% usage in primary care and 0% usage in secondary care.

a) **Based on the company's submitted base case, if GPB 1% cream is used in secondary care, it is positioned as displacing BTX. Please confirm if this is correct or explain why GPB 1% cream would not displace BTX in secondary care?**

b) **In the context of the prevalent population in secondary care who potentially may receive GPB 1% cream in that setting, please explain why the revised base case results are considered to be appropriate to**

estimate secondary care usage of GPB 1% cream if there is an assumption in the model of 0% usage of the treatment in secondary care?

c) **Please clarify why the company considers that the cost-effectiveness results for GPB 1% cream in primary care (100% usage) are appropriate to be compared with secondary care usage of oral antimuscarinics (50% secondary care usage) and BTX (100% secondary care usage).**

Response (a): For clarification, the Company's base case assumes use of GPB 1% cream within the primary care setting. As outlined in response to CQ B1, the model reflects the anticipated long-term treatment pathway. While the long-term expectation is for primary care use to become the routine setting for GPB 1% cream treatment, this does not preclude appropriate use in secondary care where clinically relevant, or its use in secondary care during earlier stages of uptake into routine clinical practice.

In response to CQ B1, a scenario analysis was also provided to explore the use of GPB 1% cream within the secondary care setting, in comparison with oxybutynin and botulinum toxin, as requested by the EAG. For patients being managed in secondary care, it is anticipated that GPB 1% cream will displace the use of oxybutynin and botulinum toxin.

Response (b): The Company's base case assumes 100% use of GPB 1% cream in primary care, which reflects the anticipated long-term treatment pathway. This assumption is based on clinical expectations that, over time, most patients will be treated with GPB 1% cream in primary care prior to any referral to secondary care. This assumption also aligns with NHS initiatives to deliver more care in the primary care setting – as reflected by the Advice and Guidance (A&G) initiative. Therefore, the model focuses on this primary care setting to capture the expected future use of GPB 1% cream.

However, we acknowledge that in the short term, and particularly for the prevalent population already under the care of secondary services, GPB 1% cream may be used in secondary care. To reflect current practice and provide a more complete view of potential usage, a scenario analysis was included in response to CQ B1. This

explored the use of GPB 1% cream in secondary care alongside relevant comparators (oxybutynin and botulinum toxin). In this scenario, GPB 1% cream remains cost-effective based on a WTP of £20,000.

In summary, while the base case assumes primary care use to reflect the anticipated long-term treatment pathway, the model and accompanying scenario analyses remain informative for understanding potential impacts across both care settings.

Response (c): The cost-effectiveness results for GPB 1% cream based on 100% primary care usage are appropriate to compare with secondary care usage of oral antimuscarinics and botulinum toxin because the introduction of GPB 1% cream is expected to shift the treatment pathway, allowing more patients to be managed in primary care. The comparator arms reflect the current treatment landscape without GPB 1% cream, where patients typically progress through available options more quickly and are referred to secondary care earlier. This is partly because only propantheline bromide is licensed for use in this indication, leading GPs to avoid prescribing alternative, unlicensed antimuscarinics. As a result, access to these treatments often requires referral to secondary care. Furthermore, the less favourable safety and tolerability profile of antimuscarinics contributes to their limited use in primary care, reinforcing the reliance on secondary care. By providing a well-tolerated, licensed treatment option earlier in the care pathway, GPB 1% cream has the potential to reduce the need for secondary care interventions. Therefore, comparing it with therapies currently used in secondary care reflects the relevant clinical and economic impact of its introduction.

A30. Priority question. Please clarify:

a) **the number of patients in Hyp1-18/2016 Phase 3a who had received prior hyperhidrosis treatments at baseline and provide a breakdown of the prior hyperhidrosis treatments received.**
b) **the number of newly recruited patients in Hyp1-18/2016 Phase 3b who had received prior hyperhidrosis treatments at baseline and provide a breakdown of the prior hyperhidrosis treatments received.**

Response (a): [redacted]

[redacted]. 7 patients are recorded as having received prior hyperhidrosis treatment in Hyp1-18/2016 Phase 3a, mainly deodorants and aluminium-containing deodorants.

Response (b): 52 of the 357 newly recruited patients for Hyp1-18/2016 Phase 3b had recorded at least 1 previous treatment for hyperhidrosis. The information in the following table is taken from the CSR appendix 16.2.4.

Table 1: 52 of the 357 newly recruited Hyp1-18/2016 Phase 3b patients that reported ≥1 previous treatment for hyperhidrosis

Patient	No.	Was (medical) treatment given for hyperhidrosis within the past 12 months before Screening?	Treatments for hyperhidrosis	Start date	Stop date	Continuing
[redacted]						

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A31. Priority question. Please provide baseline characteristics and subgroup results for: change in HDSS score from baseline (mean and median); patients with ≥2, ≥1, and 1 or 2 improvement in HDSS (a version of Table 26 in the company submission); and absolute change in total sweat production from baseline (primary endpoints in the trials; [please note, if the company is limited for time, the EAG suggests the company focuses on HDSS outcomes as HDSS is used in the economic model]):

a) **patients in Hyp1-18/2016 Phase 3a with and without prior hyperhidrosis treatment;**
b) **newly recruited patients in Hyp1-18/2016 Phase 3b with and without prior hyperhidrosis treatment.**

Response: These are analyses that have not been previously requested by regulatory or HTA assessment bodies. To provide these data would require the data holder, Dr Wolff, to re-open the analysis database. The Company is therefore unable to provide these data for the EAG.

A32. Priority question. Please explain and justify if prior hyperhidrosis therapy is considered to be a treatment effect modifier for GPB 1% cream.

Response: Sensitivity analyses have been carried out for the primary and secondary endpoints in Hyp1-18/2016 Phase 3b, excluding patients who used deodorants containing aluminium chloride and excluding patients who used deodorants that possibly contained aluminium. For the primary endpoint and all 3 key secondary endpoints, results of the sensitivity analyses were in line with results of the main analyses [CSR Tables 19, 23, 26, 29].

Section B: Clarification on treatment discontinuation scenarios

B26. Priority question: The EAG reviewed the company's oral antimuscarinic treatment discontinuation scenario supplied in response to question B19 and found a significant error that was contributing to substantial total costs estimated for the comparator. In tab "Trace_AMSC", column L, the discontinuation rate for the first 4 weeks (20.3%) is applied to every model cycle for the entire duration of the model. Instead, after week 4, a discontinuation rate of 0.2% should be applied (tab TxDuration, cell F70). Please correct the scenario and supply updated results. Please note that this scenario also affects the scenarios supplied in question B22.

Response: This error has been corrected in the "Trace_GPB", "Trace_AMSC", and "Trace_BTX" sheets (column L). During this correction, a related issue was also identified in the "TxDuration" sheet: the values in cells F16, F66, and F94 reflected hazard rates rather than per-cycle (2-week) discontinuation probabilities. These have now been corrected by converting the hazard rates to appropriate per-cycle probabilities. The updated model includes an option to apply these corrections in the "CQs" sheet under CQ B26.

The impact on the Company's revised base case results is minor - a 0.14% increase in the NMB for GPB 1% cream vs. antimuscarinics and a 0.55% increase vs. botulinum toxin. Accordingly, all scenarios and the revised base case in the CQ response have been updated to reflect these corrections (Section "Corrected

scenarios provided in Clarification response document" and Section "Corrected revised Company base case*"* respectively). The only notable changes in results are for the scenarios presented in response to CQ B19 and B22, as flagged by the EAG. These have been revised and are presented separately. Table 2, Table 3, and Table 4 below correspond to the updated versions of Tables 91, 92, and 96 from the CQ response document.

GPB 1% cream remains cost-effective at a WTP threshold of £20,000 per QALY in the scenarios presented in Table 3 and Table 4. While it is not shown to be cost-effective vs. antimuscarinics in the Table 2 scenario, this is based on an analysis requested by the EAG for which the results are not considered clinically plausible. This scenario reflects feedback from the EAG's clinical experts who estimate an overall discontinuation rate of approximately 43%, with 33% stopping in the first month and a further 10% discontinuing over an unspecified period. This estimate aligns broadly with the published literature. However, the timeframe over which discontinuation occurs is unclear. The EAG requested the scenario to assume a two-year time horizon to derive a discontinuation rate of 0.20% per cycle; the rationale for this duration was not evident. This assumption results in patients remaining on antimuscarinics for an average of 12.9 years, substantially longer than the 4.0 years estimated for GPB 1% cream. This is considered clinically implausible, as it does not align with feedback from clinical experts, who note that patients typically discontinue antimuscarinics due to poor tolerability. It is also inconsistent with published data from Wolosker et al. (2014) and Millán-Cayetano et al. (2017).[1, 2]

Importantly, the limitations of the Table 2 scenario are less relevant to the scenarios in Table 3 and Table 4, which use a two-year time horizon. This shorter horizon reduces concerns related to long-term extrapolation of treatment duration and discontinuation.

Table 2: Scenario analysis: Treatment duration for antimuscarinics informed by EAG clinical experts | Clarification Question B19a (Update of Table 91 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

Table 3: Scenario analysis: Treatment duration for antimuscarinics informed by EAG clinical experts and a 2 year time horizon | Clarification Question B19b (Update of Table 92 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

Table 4: Scenario analysis: Assuming the same HDSS response as observed for initial therapies for subsequent therapies, a 2 year time horizon, treatment discontinuation for antimuscarinics informed by EAG clinical experts and an updated approach to modelling discontinuation with botulinum toxin and assuming only formal discontinuation from Lowe et al. (2007) | Clarification Question B22bi (Update of Table 96 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

Corrected scenarios provided in Clarification response document

As highlighted in the response to CQ B26, a minor error has been identified which has been corrected in the corrected revised Company base case in Table **24** (update of Table 76 from the CQ Response document). Except for the scenarios conducted as part of CQ B19 and B22, the impact of the correction on the corrected Company's revised base case results and corrected scenarios is minor. The results specific to CQ B19 and B22 are presented and discussed in response to CQ B26. For completeness, all other scenarios provided in the CQ Response document have been updated and provided below. Note: as the correction has resulted in a minor impact on results, no commentary is provided and only corrected results are presented. The commentary remains consistent with that which was written in the CQ Response document.

CQ B1

Table 5: Scenario analysis: 100% primary care administration for GPB 1% cream vs. 100% primary care administration for propantheline bromide | Clarification Question B1a (Update of Table 77 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				
Propantheline bromide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
Note: applied to the revised Company base case.

Table 6: Scenario analysis: 100% secondary care administration for GPB 1% cream vs. 100% secondary care administration for oxybutynin 2.5mg (three times daily) and 100% secondary care administration for botulinum toxin | Clarification Question B1b (Update of Table 78 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				

Oxybutynin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

CQ B2

Table 7: Scenario analysis: 72-week time horizon | Clarification Question B2a (Update of Table 79 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

Table 8: Scenario analysis: 2-year time horizon | Clarification Question B2b (Update of Table 80 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

CQ B3

Table 9: Scenario analysis: background mortality from 2017-2019 | Clarification Question B3 (Update of Table 81 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

CQ B4

Table 10: Scenario analysis: peak efficacy for botulinum toxin at 16 weeks | Clarification Question B4 (Update of Table 82 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

CQ B6

Table 11: Scenario analysis: 20% Dysport for patients receiving two or more botulinum toxin procedures | Clarification Question B6 (Update of Table 83 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

CQB7

Table 12: Scenario analysis: 0% non-axillary sweating for botulinum toxin | Clarification Question B7 (Update of Table 84 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

CQB11

Table 13: Scenario analysis: 100% compliance with GPB 1% cream | Clarification Question B11 (Update of Table 85 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

CQ B14

Table 14: Scenario analysis: 100% secondary care administration for GPB 1% cream vs. modified-release oxybutynin 5 mg once daily | Clarification Question B14 (Update of Table 86 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				
Oxybutynin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

CQ B15

Table 15: Scenario analysis: 5% A&G administration for antimuscarinics in the first administration only | Clarification Question B15 (Update of Table 87 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

CQ B16

Table 16: Scenario analysis: Non-half-cycle-adjusted monitoring appointments for botulinum toxin | Clarification Question B16 (Update of Table 88 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

CQ B17

Table 17: Scenario analysis: Cost of £535 for the administration of botulinum toxin | Clarification Question B17 (Update of Table 89 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

CQ B18

Table 18: Scenario analysis: Primary care monitoring assumed for GPB 1% cream and antimuscarinics and no monitoring costs for botulinum toxin | Clarification Question B18 (Update of Table 90 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

CQ B19

For the results to CQ B19a and B19b, see Table 2 and Table 3 in response to CQ B26.

CQ B20

Table 19: Scenario analysis: Updated approach to modelling discontinuation with botulinum toxin | Clarification Question B20a (Update of Table 93 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Table 20: Scenario analysis: Updated approach to modelling discontinuation with botulinum toxin and assuming only formal discontinuations from Lowe et al. (2007) | Clarification Question B20b (Update of Table 94 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

CQ B22

Table 21: Scenario analysis: Assuming the same HDSS response as observed for initial therapies for subsequent therapies and a 2 year time horizon | Clarification Question B22b (Update of Table 95 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Note: applied to the revised Company base case.

For the results to CQ B22bi, see Table 4 in response to CQ B26.

CQ B24

Table 22: Scenario analysis: Assuming subsequent therapy distribution based on EAG's clinical feedback and assuming the same HDSS response as observed for initial therapies for subsequent therapies | Clarification Question B24a (Update of Table 98 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)		Incremental QALYs	ICER (£/QALY)	NMB (WTP £20,000)
GPB 1% cream	[redacted]	[redacted]					
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Table 23: Scenario analysis: Assuming subsequent therapy distribution based on EAG's clinical feedback, assuming the same HDSS response as observed for initial therapies for subsequent therapies, and a 2 year time horizon | Clarification Question B24b (Update of Table 99 from CQ response document)

Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£/QALY)**	**NMB (WTP £20,000)**
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years; WTP, willingness-to-pay.
Note: applied to the revised Company base case.

Corrected revised Company base case

As reported in the CQ Response document, the Company revised its base case in response to the following questions:

- CQ B9 - the cost of non-axillary sweating/HH has been corrected
- CQ B12 – the cost of propantheline bromide has been updated to £20.74
- CQ B21 – the hardcoded values from the calculation of subsequent therapies has been removed

As highlighted in the response to CQ B26, a minor error was also identified which has been corrected in the corrected revised Company base case in Table 24 (update of Table 76 from the CQ Response document). The impact of the correction on the Company's revised base case results is minor - a 0.14% increase in the NMB for GPB 1% cream vs. antimuscarinics and a 0.55% increase vs. botulinum toxin.

All scenarios (Section "*Corrected scenarios provided in Clarification response document*") and the revised base case in the CQ response have been updated to reflect these corrections.

Table 24**: Step changes from original Company base case to revised Company base case (Update of Table 76 from CQ response document)**

	Vs. Antimuscarinics		Vs. Botulinum toxin	
	ICER	**NMB**	**ICER**	**NMB**
Original Company base case	Dominant	[redacted]	Dominant	[redacted]
Correction from CQ B9	Dominant	[redacted]	Dominant	[redacted]
Updated propantheline bromide cost from CQ B12	Dominant	[redacted]	Dominant	[redacted]
Removed hard coded values from subsequent therapies	Dominant	[redacted]	Dominant	[redacted]
Corrected hazard rates to per-cycle (2-week) discontinuation probabilities	Dominant	[redacted]	Dominant	[redacted]
Corrected revised Company base case	**Dominant**	[redacted]	**Dominant**	[redacted]

Abbreviations: CQ, clarification question; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit

Corrected revised base-case results

Table 25 presents the corrected revised base case pairwise results vs. GPB 1% cream and Table **26** presents the corrected revised incremental analysis. presents the corresponding revised net health benefits (NHBs) vs. GPB 1% cream.

Note: as the correction has resulted in a minor impact on results, no commentary is provided and only corrected results are presented. The commentary remains consistent with that which was written in the CQ Response document.

GPB 1% cream vs. antimuscarinics

In the revised base case analysis, GPB 1% cream generates [redacted] additional QALYs at a reduced cost of [redacted] compared to antimuscarinics. The NHB is [redacted] at a WTP threshold of £20,000, and [redacted] at a threshold of £30,000. Corresponding NMBs are [redacted] and [redacted], respectively.

GPB 1% cream vs. botulinum toxin

In the base case analysis, GPB 1% cream generates [redacted] additional QALYs at a reduced cost of [redacted] compared to botulinum toxin. The NHB is [redacted] at a WTP threshold of £20,000, and [redacted] at a threshold of £30,000. Corresponding NMBs are [redacted] and [redacted], respectively.

Table 25: Revised base-case results vs. GPB 1% cream (Update of Table 100 from CQ response document)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
GPB 1% cream	[redacted]	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 26: Revised incremental analysis (Update of Table 101 from CQ response document)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
GPB 1% cream	[redacted]	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 27: Revised net health benefit vs. GPB 1% cream (Update of Table 102 from CQ response document)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

Corrected revised sensitivity analyses

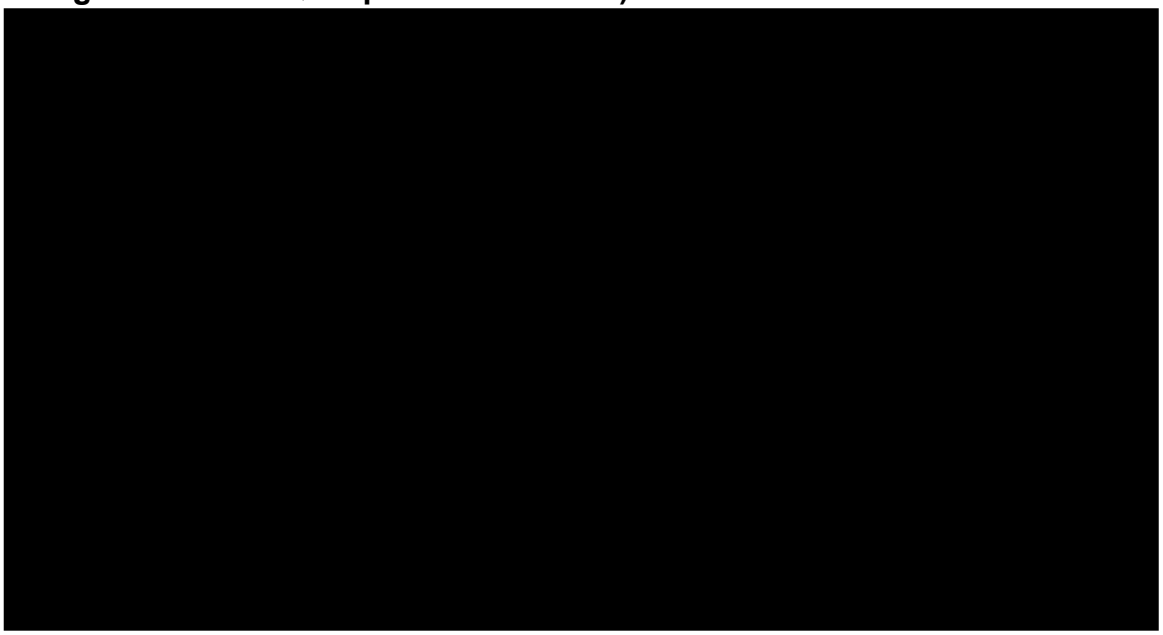
Probabilistic sensitivity analysis

The proportion of PSA iterations where GPB 1% cream is considered cost-effective is [redacted] at a £20,000/QALY threshold. The CEAC is shown in Figure 1. The convergence plots for the PSA for vs. antimuscarinics and vs. botulinum toxin are presented in Figure 2 and Figure 3, respectively, based on the NMB endpoint.

Figure 1: Revised CEAC (Update of Figure 5 from CQ response document)

Abbreviations: CEAC, cost-effectiveness acceptability curve; GPB, glycopyrronium bromide.

Figure 2: PSA convergence plot for GPB 1% cream vs. antimuscarinics (Update of Figure 6 from CQ response document)



Abbreviations: GPB, glycopyrronium bromide; NMB, net monetary benefit; PSA, probabilistic sensitivity analysis

Figure 3: PSA convergence plot for GPB 1% cream vs. botulinum toxin (Update of Figure 7 from CQ response document)

Abbreviations: GPB, glycopyrronium bromide; NMB, net monetary benefit; PSA, probabilistic sensitivity analysis

GPB 1% cream vs. antimuscarinics

The PSA results indicate an average incremental cost of [redacted] and an average incremental QALY gain of [redacted] for GPB 1% cream compared to antimuscarinics. These results are consistent with the deterministic analysis, confirming that GPB 1%

cream is dominant (i.e., more effective and less costly). This consistency is visually supported by the overlap of the deterministic and probabilistic base case markers in the cost-effectiveness plane (Figure 4).

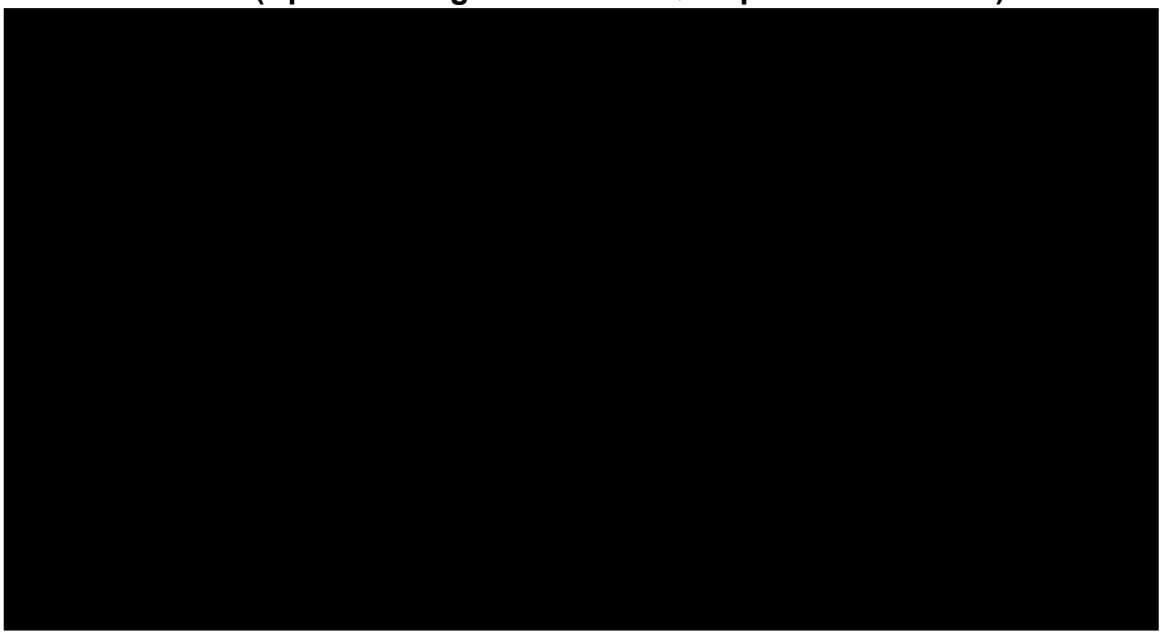
Figure 4: Revised cost-effectiveness plane (1,000 iterations) | GPB 1% cream vs. antimuscarinics (Update of Figure 8 from CQ response document)

Abbreviations: GPB, glycopyrronium bromide; QALY, quality adjusted life year; WTP, willingness-to-pay.

GPB 1% cream vs. botulinum toxin

For the comparison with botulinum toxin, the PSA shows an average incremental cost of [redacted] and an average incremental QALY gain of [redacted] for GPB 1% cream. Again, the probabilistic results are aligned with the deterministic findings, indicating dominance of GPB 1% cream. This is further evidenced by the overlap in the deterministic and probabilistic results on the cost-effectiveness plane (Figure 5).

Figure 5: Revised cost-effectiveness plane (1,000 iterations) | GPB 1% cream vs. botulinum toxin (Update of Figure 9 from CQ response document)



Abbreviations: GPB, glycopyrronium bromide; QALY, quality adjusted life year; WTP, willingness-to-pay.

Deterministic sensitivity analysis

GPB 1% cream vs. antimuscarinics

Results for the ten most influential parameters for GPB 1% cream vs. antimuscarinics are shown in Table 28 and depicted in a tornado diagram in Figure 6 and Figure 7 based on the ICER and a NMB with a WTP of £20,000, respectively.

Table 28: Top ten parameters impacting the ICER (revised one-way sensitivity analysis) | GPB 1% cream vs. antimuscarinics (Update of Table 103 from CQ response document)

Parameter	Lower bound	Upper bound	Difference
Antimuscarinics: 2-week proportion of AEs, Non-axillary sweating/hyperhidrosis	[redacted]	[redacted]	[redacted]
Utilities HDSS=4	[redacted]	[redacted]	[redacted]
Antimuscarinics: proportion Unlicensed GPB (secondary care)	[redacted]	[redacted]	[redacted]
Antimuscarinics: Proportion of discontinuations 0-26 weeks	[redacted]	[redacted]	[redacted]
Antimuscarinics: proportion Botulinum toxin (secondary care) subsequent therapy	[redacted]	[redacted]	[redacted]

Utilities HDSS=3	[redacted]	[redacted]	[redacted]
GPB 1% cream: Proportion of discontinuations 0-72 weeks	[redacted]	[redacted]	[redacted]
GPB 1% cream: proportion Botulinum toxin (secondary care) subsequent therapy	[redacted]	[redacted]	[redacted]
Utilities HDSS=2	[redacted]	[redacted]	[redacted]
Antimuscarinics: 2-week proportion of AEs, Dry mouth	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; ICER, incremental cost-effectiveness ratio.

Figure 6: Tornado plot, ICER (revised one-way sensitivity analysis) | GPB 1% cream vs. antimuscarinics (Update of Figure 10 from CQ response document)

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; ICER, incremental cost-effectiveness ratio.

Figure 7: Tornado plot, NMB at a WTP of £20,000 (revised one-way sensitivity analysis) | GPB 1% cream vs. antimuscarinics (Update of Figure 11 from CQ response document)

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; NMB, net monetary benefit; WTP, willingness-to-pay.

GPB 1% cream vs. botulinum toxin

Results for the ten most influential parameters for GPB 1% cream vs. botulinum toxin are shown in Table 29 and depicted in a tornado diagram in Figure 8 and Figure 9 based on the ICER and a NMB with a WTP of £20,000, respectively.

Table 29: Top ten parameters impacting the ICER (revised one-way sensitivity analysis) | GPB 1% cream vs. botulinum toxin (Update of Table 104 from CQ response document)

Parameter	Lower bound	Upper bound	Difference
Utilities HDSS=4	[redacted]	[redacted]	[redacted]
Utilities HDSS=3	[redacted]	[redacted]	[redacted]
Utilities HDSS=2	[redacted]	[redacted]	[redacted]
Subsequent therapy costs: unlicensed GPB (secondary care)	[redacted]	[redacted]	[redacted]
Botulinum toxin: proportion unlicensed GPB (secondary care) subsequent therapy	[redacted]	[redacted]	[redacted]
Botulinum toxin: Proportion of discontinuations 0-26 weeks	[redacted]	[redacted]	[redacted]
Unlicensed GPB: cost per tube	[redacted]	[redacted]	[redacted]
Subsequent therapy costs: Botulinum toxin (secondary care)	[redacted]	[redacted]	[redacted]
Utilities HDSS=1	[redacted]	[redacted]	[redacted]
Number of Botulinum toxin procedures per year	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; ICER, incremental cost-effectiveness ratio.

Figure 8: Tornado plot, ICER (revised one-way sensitivity analysis) | GPB 1% cream vs. botulinum toxin (Update of Figure 12 from CQ response document)

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; ICER, incremental cost-effectiveness ratio.

Figure 9: Tornado plot, NMB at a WTP of £20,000 (revised one-way sensitivity analysis) | GPB 1% cream vs. botulinum toxin (Update of Figure 13 from CQ response document)

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; NMB, net monetary benefit; WTP, willingness-to-pay.

Scenario analysis

Scenario analyses were conducted to assess structural uncertainty within the economic model. The corresponding results from the deterministic analyses for GPB 1% cream vs. antimuscarinics are shown in Table 30 and Table 31 for the ICER and NMB with a WTP of £20,000, respectively. For GPB 1% cream vs. botulinum toxin these are shown in Table 32 and Table 33, respectively.

GPB 1% cream vs. antimuscarinics

Table 30: Revised deterministic scenario analyses (ICER) | GPB 1% cream vs. antimuscarinics (Update of Table 105 from CQ response document)

Scenario name	ICER	% change from base case
Base case	[redacted]	NA
Time horizon: 4-years	[redacted]	1617.0%
Time horizon: 5-years	[redacted]	1026.9%
Time horizon: 10-years	[redacted]	179.0%
Half cycle correction: excluded	[redacted]	26.2%
Discount rate: 0% costs and 0% outcomes	[redacted]	-283.8%
Baseline characteristics: FASa	[redacted]	3.0%
Baseline characteristics: PPSb	[redacted]	1.4%
Baseline GPB 1% cream efficacy: PPSb	[redacted]	-23.3%
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	-23.1%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on PPSa	[redacted]	-1.1%

Scenario name	ICER	% change from base case
Relative efficacy of GPB 1% cream vs. antimuscarinics based on Wade et al. (2017)	[redacted]	-0.9%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on PPSa	[redacted]	0.0%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on Wade et al. (2017)	[redacted]	0.0%
Relative efficacy of GPB 1% cream vs. botulinum toxin ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	0.0%
Dose of botulinum toxin assumed 150U	[redacted]	8.7%
Dose of botulinum toxin assumed combined of 100U and 150U	[redacted]	4.4%
Relative efficacy for 2+ botulinum toxin procedures based on Lowe et al. (2007)	[redacted]	0.0%
Relative efficacy for 2+ botulinum toxin procedures based on a 10% reduction in OR	[redacted]	0.0%
Relative efficacy for 2+ botulinum toxin procedures based on a 20% reduction in OR	[redacted]	0.0%
Maximum botulinum toxin efficacy achieved at week 8	[redacted]	0.0%
Maximum botulinum toxin efficacy achieved at week 12	[redacted]	0.0%
1.8 botulinum procedures per year	[redacted]	0.7%
Cost of propantheline bromide of £20.74	[redacted]	0.0%
Dose per day of oxybutynin of 12.5mg	[redacted]	4.8%

Scenario name	ICER	% change from base case
Dose intensity for oral antimuscarinics assumed equal to GPB 1% cream	[redacted]	-120.6%
Increase in discontinuation rate with GPB 1% cream of 10%	[redacted]	55.4%
Increase in discontinuation rate with GPB 1% cream of 20%	[redacted]	108.3%
Source of discontinuation for antimuscarinics from Millan-Cayetano et al. (2017)	[redacted]	17954.5%
Discontinuation for botulinum toxin assumed as only those who were formally discontinued	[redacted]	49.8%
Discontinuation for botulinum toxin assumed as those who were formally discontinued and no further treatment	[redacted]	-9.8%

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; GPB, glycopyrronium bromide; NMB, net monetary benefit; PPS, per-protocol set; WTP, willingness-to-pay.

Table 31: Revised deterministic scenario analyses (NMB based on a £20,000 WTP) | GPB 1% cream vs. antimuscarinics (Update of Table 106 from CQ response document)

Scenario name	NMB	% change from base case
Base case	[redacted]	NA
Time horizon: 4-years	[redacted]	-21.3%
Time horizon: 5-years	[redacted]	-16.0%
Time horizon: 10-years	[redacted]	-3.9%
Half cycle correction: excluded	[redacted]	0.7%
Discount rate: 0% costs and 0% outcomes	[redacted]	7.6%
Baseline characteristics: FASa	[redacted]	-0.8%
Baseline characteristics: PPSb	[redacted]	-0.3%
Baseline GPB 1% cream efficacy: PPSb	[redacted]	29.6%

Scenario name	NMB	% change from base case
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	29.2%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on PPSa	[redacted]	1.1%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on Wade et al. (2017)	[redacted]	0.9%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on PPSa	[redacted]	0.0%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on Wade et al. (2017)	[redacted]	0.0%
Relative efficacy of GPB 1% cream vs. botulinum toxin ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	0.0%
Dose of botulinum toxin assumed 150U	[redacted]	0.2%
Dose of botulinum toxin assumed combined of 100U and 150U	[redacted]	0.1%
Relative efficacy for 2+ botulinum toxin procedures based on Lowe et al. (2007)	[redacted]	0.0%
Relative efficacy for 2+ botulinum toxin procedures based on a 10% reduction in OR	[redacted]	0.0%
Relative efficacy for 2+ botulinum toxin procedures based on a 20% reduction in OR	[redacted]	0.0%
Maximum botulinum toxin efficacy achieved at week 8	[redacted]	0.0%
Maximum botulinum toxin efficacy achieved at week 12	[redacted]	0.0%
1.8 botulinum procedures per year	[redacted]	0.0%
Cost of propantheline bromide of £20.74	[redacted]	0.0%
Dose per day of oxybutynin of 12.5mg	[redacted]	0.1%
Dose intensity for oral antimuscarinics assumed equal to GPB 1% cream	[redacted]	-3.1%

Scenario name	NMB	% change from base case
Increase in discontinuation rate with GPB 1% cream of 10%	[redacted]	-6.7%
Increase in discontinuation rate with GPB 1% cream of 20%	[redacted]	-12.2%
Source of discontinuation for antimuscarinics from Millan-Cayetano et al. (2017)	[redacted]	-33.7%
Discontinuation for botulinum toxin assumed as only those who were formally discontinued	[redacted]	1.3%
Discontinuation for botulinum toxin assumed as those who were formally discontinued and no further treatment	[redacted]	-0.3%

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; GPB, glycopyrronium bromide; NMB, net monetary benefit; PPS, per-protocol set; WTP, willingness-to-pay.

GPB 1% cream vs. botulinum toxin

Table 32: Revised deterministic scenario analyses (ICER) | GPB 1% cream vs. botulinum toxin (Update of Table 107 from CQ response document)

Scenario name	ICER	% change from base case
Base case	[redacted]	NA
Time horizon: 20-years	[redacted]	88.8%
Time horizon: 40-years	[redacted]	60.0%
Time horizon: 60-years	[redacted]	10.6%
Half cycle correction: excluded	[redacted]	1.2%
Discount rate: 0% costs and 0% outcomes	[redacted]	-23.3%
Baseline characteristics: FASa	[redacted]	1.0%
Baseline characteristics: PPSb	[redacted]	0.4%
Baseline GPB 1% cream efficacy: PPSb	[redacted]	-31.7%
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	-22.1%

Scenario name	ICER	% change from base case
Relative efficacy of GPB 1% cream vs. antimuscarinics based on PPSa	[redacted]	1.5%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on Wade et al. (2017)	[redacted]	4.6%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on PPSa	[redacted]	-2.7%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on Wade et al. (2017)	[redacted]	0.3%
Relative efficacy of GPB 1% cream vs. botulinum toxin ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	4.6%
Dose of botulinum toxin assumed 150U	[redacted]	1.8%
Dose of botulinum toxin assumed combined of 100U and 150U	[redacted]	0.9%
Relative efficacy for 2+ botulinum toxin procedures based on Lowe et al. (2007)	[redacted]	4.7%
Relative efficacy for 2+ botulinum toxin procedures based on a 10% reduction in OR	[redacted]	-0.9%
Relative efficacy for 2+ botulinum toxin procedures based on a 20% reduction in OR	[redacted]	-1.8%
Maximum botulinum toxin efficacy achieved at week 8	[redacted]	8.6%
Maximum botulinum toxin efficacy achieved at week 12	[redacted]	15.5%
1.8 botulinum procedures per year	[redacted]	4.7%
Cost of propantheline bromide of £20.74	[redacted]	0.0%
Dose per day of oxybutynin of 12.5mg	[redacted]	0.1%
Dose intensity for oral antimuscarinics assumed equal to GPB 1% cream	[redacted]	-2.6%
Increase in discontinuation rate with GPB 1% cream of 10%	[redacted]	5.2%
Increase in discontinuation rate with GPB 1%	[redacted]	10.2%

Scenario name	ICER	% change from base case
cream of 20%		
Source of discontinuation for antimuscarinics from Millan-Cayetano et al. (2017)	[redacted]	42.9%
Discontinuation for botulinum toxin assumed as only those who were formally discontinued	[redacted]	414.4%
Discontinuation for botulinum toxin assumed as those who were formally discontinued and no further treatment	[redacted]	-36.4%

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; GPB, glycopyrronium bromide; NMB, net monetary benefit; PPS, per-protocol set; WTP, willingness-to-pay.

Table 33: Revised deterministic scenario analyses (NMB based on a £20,000 WTP) | GPB 1% cream vs. botulinum toxin (Update of Table 108 from CQ response document)

Scenario name	NMB	% change from base case
Base case	[redacted]	NA
Time horizon: 20-years	[redacted]	-24.3%
Time horizon: 40-years	[redacted]	-18.1%
Time horizon: 60-years	[redacted]	-4.6%
Half cycle correction: excluded	[redacted]	0.3%
Discount rate: 0% costs and 0% outcomes	[redacted]	6.3%
Baseline characteristics: FASa	[redacted]	-0.7%
Baseline characteristics: PPSb	[redacted]	-0.3%
Baseline GPB 1% cream efficacy: PPSb	[redacted]	31.7%
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	19.4%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on PPSa	[redacted]	-1.0%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on Wade et al. (2017)	[redacted]	-3.0%

Scenario name	NMB	% change from base case
Relative efficacy of GPB 1% cream vs. botulinum toxin based on PPSa	[redacted]	1.9%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on Wade et al. (2017)	[redacted]	-0.2%
Relative efficacy of GPB 1% cream vs. botulinum toxin ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	-3.0%
Dose of botulinum toxin assumed 150U	[redacted]	1.0%
Dose of botulinum toxin assumed combined of 100U and 150U	[redacted]	0.5%
Relative efficacy for 2+ botulinum toxin procedures based on Lowe et al. (2007)	[redacted]	-3.0%
Relative efficacy for 2+ botulinum toxin procedures based on a 10% reduction in OR	[redacted]	0.6%
Relative efficacy for 2+ botulinum toxin procedures based on a 20% reduction in OR	[redacted]	1.3%
Maximum botulinum toxin efficacy achieved at week 8	[redacted]	-5.4%
Maximum botulinum toxin efficacy achieved at week 12	[redacted]	-9.2%
1.8 botulinum procedures per year	[redacted]	-1.5%
Cost of propantheline bromide of £20.74	[redacted]	0.0%
Dose per day of oxybutynin of 12.5mg	[redacted]	0.0%
Dose intensity for oral antimuscarinics assumed equal to GPB 1% cream	[redacted]	-0.8%
Increase in discontinuation rate with GPB 1% cream of 10%	[redacted]	-6.1%
Increase in discontinuation rate with GPB 1% cream of 20%	[redacted]	-11.0%
Source of discontinuation for antimuscarinics from Millan-Cayetano et al. (2017)	[redacted]	13.6%
Discontinuation for botulinum toxin assumed as	[redacted]	-12.7%

Scenario name	NMB	% change from base case
only those who were formally discontinued		
Discontinuation for botulinum toxin assumed as those who were formally discontinued and no further treatment	[redacted]	1.0%

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; GPB, glycopyrronium bromide; NMB, net monetary benefit; PPS, per-protocol set; WTP, willingness-to-pay.

References

1. Millán-Cayetano JF, Del Boz J, Rivas-Ruiz F, Blázquez-Sánchez N, Hernández Ibáñez C, de Troya-Martín M. Oral oxybutynin for the treatment of hyperhidrosis: outcomes after one-year follow-up. *Australas J Dermatol*. 2017;58(2):e31–e35. https://doi.org/10.1111/ajd.12473.
2. Wolosker N, Teivelis MP, Krutman M, *et al.* Long-term results of the use of oxybutynin for the treatment of axillary hyperhidrosis. *Ann Vasc Surg*. 2014;28(5):1106–1112. https://doi.org/10.1016/j.avsg.2013.12.024.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Glycopyrronium bromide cream for treating severe primary axillary hyperhidrosis [ID6487]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted], [redacted] on behalf of the British Association of Dermatologists' Therapy & Guidelines Sub-committee
2. Name of organisation	British Association of Dermatologists
3. Job title or position	Consultant Dermatologists
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes ~~or No~~ A specialist in the treatment of people with this condition? Yes ~~or No~~ A specialist in the clinical evidence base for this condition or technology? Yes ~~or No~~ Other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD is a not-for-profit organisation whose charitable objectives are the practice, teaching, training, and research of dermatology. It works with the Department of Health, patient bodies and commissioners across the UK, advising on best practice and the provision of dermatology services across all service settings. It is funded by the activities of its members.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To significantly reduce sweating associated with severe, primary axillary hyperhidrosis (PAHH).
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Variable access to the limited effective treatments that exist – please see the next section.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Currently, severe PAHH is treated using a range of options, however, their availability varies greatly across regions and many treatments can cause adverse side effects. Not all treatments are currently used in the NHS, except: • Antiperspirants containing aluminium salts – widely available and often the first treatment option. • Oral antimuscarinics such as oral propantheline – prescribed for patients who do not respond to topical treatments. Other treatment options may include: • Oral glycopyrronium bromide may be used but its availability varies; in some regions, it is not on the local drugs formulary, while in others, it is only available through hospital dermatologists, leading to increased demand on NHS dermatology services and potential inconvenience for patients needing hospital visits. • Off-label oxybutynin is sometimes prescribed by GPs when patients cannot tolerate or do not respond to topical antiperspirants. • Off-label beta-blockers, anxiolytics, and antihypertensives may be used in managing hyperhidrosis, particularly if anxiety is a contributing factor, but many dermatologists may not be comfortable or familiar with prescribing them for hyperhidrosis. Procedural and surgical options: • Iontophoresis is not available in all NHS dermatology departments. As such, patients may need to purchase or rent their own iontophoresis machine and axillary pads. • Botulinum toxin injections are not widely accessible in NHS dermatology departments. • Surgical options (sweat gland ablation and thoracic sympathectomy) may not be available in all NHS trusts and are rarely chosen due to risks such as rebound sweating and compensatory sweating in other areas. It is crucial to note that access to treatments varies greatly, and some patients face challenges in obtaining certain medications or specialist treatments within the NHS.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	No.

9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	No.
9c. What impact would the technology have on the current pathway of care?	Topical glycopyrronium bromide cream would provide an additional treatment option for patients who do not respond to or cannot tolerate topical antiperspirants (including aluminium hexahydrate). This could offer a non-invasive alternative before progressing to more complex – or difficult to access – treatments, such as iontophoresis, oral treatments, or surgical interventions. 1. Glycopyrronium bromide cream can be used in the same way as other topical treatments for HH being prescribed in primary care. 2. While short-term iontophoresis trials are available in some NHS dermatology departments, long-term use often requires patients to purchase or rent machines and buy axillary pads, which can be costly and difficult to use. Thus, an effective, licensed, alternative could potentially reduce the need for iontophoresis. 3. Surgery is rarely performed due to the risks associated with the procedures and risks of rebound sweating at the same site or compensatory hyperhidrosis at other sites with procedures such as endoscopic thoracic sympathectomy.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Glycopyrronium bromide cream can be used in the same way as other topical treatments for hyperhidrosis, i.e. they are usually prescribed in primary care.
10a. How does healthcare resource use differ between the technology and current care?	Healthcare resource use differs significantly between this technology and current prescribing of topical glycopyrronium bromide, due to prescribing and administrative challenges associated with how this technology is currently being prescribed. Currently, clinicians wishing to prescribe topical glycopyrronium bromide must order the medicine as a "special" product, which is a time-consuming and complex process. Ordering specials involves additional paperwork,

	justification of cost and follow-ups with the local prescribing formulary – this is problematic, because many GPs would be reluctant to prescribe treatments that do not have a "green status" on local prescribing formularies. In contrast, if glycopyrronium bromide cream were both licensed *and* recommended by NICE, it could be prescribed in primary care in the same way as existing topical treatments for PAHH. This could potentially remove the administrative burden and reduce delays in patient access to treatment.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Primary care - for equitable access, and also because this topical treatment is not associated with significant adverse effects that need close monitoring in a hospital setting.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Topical glycopyrronium bromide could offer a non-invasive, targeted option before systemic, procedural or surgical treatments need to be considered.
11a. Do you expect the technology to increase length of life more than current care?	N/A

11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. Severe PAHH significantly affects patients' quality of life, interfering with daily activities and causing anxiety and embarrassment. Topical glycopyrronium bromide has the potential to improve health-related quality of life by addressing both the physical discomfort and the psychosocial burdens caused by severe axillary hyperhidrosis. 1. Reducing excessive underarm sweating could help prevent skin irritation and discomfort caused by damp clothing and irritant dermatitis in the axillary area. 2. Many people with axillary hyperhidrosis frequently change clothes and restrict their wardrobe to dark-coloured clothing to hide sweat stains. Better control of sweating could, in turn, reduce the need for such burdensome coping strategies. 3. Excessive sweating is often associated with increased self-consciousness, particularly in social or professional settings where physical exertion or stress (e.g. work meetings, presentations) can exacerbate symptoms. Thus, the reduction of sweating could help reduce anxiety, leading to a better, overall quality of life.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	None that we are of.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical	Nil expected – this is a topical treatment and likely to carry the same risk of local irritation compared to topical aluminium deodorants.

requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes. One significant health-related benefit that may not be fully captured in QALY calculations is the improvement of patients' ability to maintain employment and participate more fully in daily life. Patients with severe PAHH frequently report the need to take time off work due to embarrassment, discomfort, or the need for frequent clothing changes. Effective treatment could help reduce severe PAHH symptoms, social anxiety, thus enabling patients to fully participate in the workforce and daily social interactions. While these improvements may not directly translate into QALY benefits, they have a significant impact on a person's quality of life, emotional wellbeing, and self-esteem. Furthermore, improved ability to work consistently may reduce indirect costs of employers such as lost productivity and have positive ripple effects within workplaces and the wider economy. Kamoudoni *et al.* reported that "33% reported choosing careers to accommodate their sweating. One participant declined the opportunity to become a policeman 'settling for a boring office job" instead.'" https://pubmed.ncbi.nlm.nih.gov/28595584/.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the	Yes. Topical glycopyrronium bromide cream would provide an additional treatment option, prescribable in primary care, for patients who do not respond to or cannot tolerate topical antiperspirants (including aluminium hexahydrate). This could offer a non-invasive alternative before progressing to more complex – or difficult to access – treatments, such as iontophoresis, oral treatments, or surgical interventions.

way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Low risk – potential for local irritation.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Currently, UK practice varies greatly depending on what treatments are available and also whether PAHH patients are being seen at all due to pressures on the system, such as from the provision of skin cancer services. There are probably not many departments across the four nations who order specials containing glycopyrronium bromide due to costs, paperwork, follow-up burden, etc. – many GPs will not order and prescribe specials as they are not on the area prescribing formulary.
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are health- or hyperhidrosis-related quality of life outcome measures. They were measured in the phase 3a (Abels *et al.* 2021) and 3b trials (Szeimies *et al.* 2023). Measuring absolute changes in sweat production using gravimetric measurements would be difficult to implement in busy NHS hospitals or GP settings.

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that we are aware of beyond those reported in the aforementioned phase 3a (Abels *et al.* 2021) and 3b trials (Szeimies *et al.* 2023) of 1% glycopyrronium bromide cream in patients with severe PAHH.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	None that we are aware of.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	There is little real-world experience as very few dermatologists prescribe specials containing glycopyrronium bromide due to the obstacles mentioned above.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None that we are aware of.
22b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions

23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Topical glycopyrronium bromide is a safe and efficacious topical treatment that can be implemented in primary care and is less likely to be associated with adverse effects compared with systemic anticholinergic drugs such as oral oxybutynin, propantheline or glycopyrronium bromide – not just dry mouth but central nervous system (CNS) adverse side effects which can impact patients at risk of cognitive decline more severely. • Topical glycopyrronium bromide can be prescribed in the same way as existing topical treatments for PAHH being prescribed in primary care. This would remove the administrative burden associated with "special" orders in secondary care and greatly reduces waiting times for treatment. • Topical glycopyrronium bromide can greatly contribute to improving patients' quality of life, with a potentially positive ripple effect on their workplace and the economy in general. • Topical glycopyrronium bromide can be prescribed in primary care, thus reducing waiting times for treatment for patients, and waiting lists for secondary care.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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Please select YES if you would like to receive information about other NICE topics - YES or NO

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Glycopyrronium bromide cream for treating severe primary axillary hyperhidrosis [ID6487]

NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Cornwall & IoS ICB
3. Job title or position	Pharmacist

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	ICB
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	We have local guidelines for Hyperhidrosis based on Primary care Dermatology Society
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway is defined as to what to try first/second and then to refer for possibility of iontophoresis Botulinum toxin is NOT available
8. What impact would the technology have on the current pathway of care?	If deemed by NICE to be value for money, then it would potentially have a useful place as GP prescribed licensed item.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	Not being used currently
10. Will the technology be used (or is it already used) in the same way	Yes as a possible first/second line/third line before referral. How severe hyperhidrosis is defined will be important.

as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	Cost of treatments used in primary care are likely to be less than this this new product
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Primary care
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	How severe hyperhidrosis is defined will be important and how to judge whether it has been effective for the patient.
11. What is the outcome of any evaluations or audits of the use of the technology?	What outcomes measures can be easily used by patients and HCP if this is approved to ascertain whether treatment is working? Those in the scope are not very helpful in a busy GP setting.

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	Is this for adults or children and young people?
12b. Consider whether these issues are different from issues with current care and why.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

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BMJ TAG

Glycopyrronium bromide cream for treating severe primary axillary hyperhidrosis [ID6487]

STA Report

Source of funding

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Title:	Glycopyrronium bromide cream for treating severe primary axillary hyperhidrosis [ID6487]
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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Nicole Downes	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Kate Ennis	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the EAG report.

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List of Abbreviations

A&G	Advice and guidance
ADR	Adverse drug reaction
AE	Adverse event
AHH	Axillary hyperhidrosis
AI	Activity impairment
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BDRM	Blind data review meeting
BL	Baseline
BMI	Body mass index
BNF	British National Formulary
BSA	Body surface area
BTX	Botulinum toxin
CCA	Cost comparison analysis
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CI	Confidence interval
CSR	Clinical study report
DLQI	Dermatology Life Quality Index
EAG	External Assessment Group
EC	Exclusion criteria
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
EQ-5D	EuroQol- 5 Dimension
ETS	Endoscopic thoracic sympathectomy
EU	European Union
FAS	Full analysis set
FU	Follow-up
GBP	Great British Pound
GI	Gastrointestinal
GM	Gravimetric measurement
GP	General practitioners
GPB	Glycopyrronium bromide
HDSS	Hyperhidrosis Disease Severity Scale
HH	Hyperhidrosis
HidroQoL	Hyperhidrosis Quality of Life Index

HRG	Healthcare Resource Group
HRQoL	Health-related Quality of Life
HTA	Health Technology Assessment
IC	Inclusion criterion
ICER	Incremental cost-effectiveness ratio
IMP	Investigational medicinal product
ITC	Indirect treatment comparison
LYG	Life years gained
mAChR	Muscarinic acetylcholine receptors
MCID	Minimally clinically important difference
MedDRA	Medical dictionary for regulatory activities
Mg	Milligram
Min	Minute
ML	Millilitres
N	Number
NA	Non-applicable
NICE	National Institute for Health and Care Excellence
NHB	Net health benefits
PAHH	Primary Axillary Hyperhidrosis
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted Life Year
QoL	Quality of Life
RCT	Randomised controlled trials
SAE	Serious adverse event
SAF	Safety analysis set
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single technology appraisal
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment emergent adverse event
U	Units
UK	United Kingdom
US	United States
WKS	Weeks

1 Executive summary

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 presents a summary of the EAG's key issues on the evidence submitted on the clinical and cost-effectiveness of glycopyrronium bromide (GPB) 1% cream for treating severe primary axillary hyperhidrosis (PAHH).

Table 1. Summary of key issues

ID	Summary of issue	Impact on results	Report sections
1	Population in the Hyp-18/2016 Phase 3a and 3b trial does not align with the company's proposed positioning for GPB 1% cream	Unknown	2.3.1 and 3.2
2	Cost-effectiveness analysis not stratified by primary care and secondary care setting	Large	2.3.2 and 4.2.4.1
3	Lack of correlation between sweat production and HDSS score	Unknown	3.3.2
4	Uncertainty in the indirect treatment comparisons	Unknown	3.4
5	Utility values used for HDSS health states	Large	4.2.6.2
6	Lifetime horizon of the economic model is potentially too long	Large	4.2.2.1
7	Assumptions around treatment waning for botulinum toxin A	Medium	4.2.3.3
8	Inclusion of the impact of adverse events on costs and QALYs	Large	4.2.5.1
9	Monitoring costs of oral antimuscarinics	Medium	4.2.7.4
10	Monitoring costs of botulinum toxin A	Medium	4.2.7.4
11	Treatment discontinuation of oral antimuscarinics	Large	4.2.7.6
12	Treatment discontinuation of botulinum toxin A	Large	4.2.7.6
13	Exclusion of QALY benefit of subsequent treatments	Large	4.2.8.1
14	Basket of subsequent treatment assumed for each treatment arm	Low	4.2.8.1

Abbreviations: EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; NHS, National Health Service; QALY, quality-adjusted life-year.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- Separating the cost-effectiveness analysis results by primary care and secondary care settings.
- Using the drug tariff price instead of the short-term concessionary price for propantheline bromide.
- Changing the treatment effectiveness assumptions for botulinum toxin A to reflect the latest evidence and the EAG's clinical expert's experience of the treatment.
- Removing the impact of [redacted] adverse events from the economic model.
- Reducing the monitoring costs of comparator treatments to reflect the EAG's clinical expert's experience of using the treatments in the NHS.
- Reducing the rate of discontinuation of comparator treatments in line with the EAG's clinical expert's experience of using the treatments in the NHS.

- Assuming that subsequent treatments result in improvements in patient's health-related quality of life (HRQoL).
- Assuming different proportions of subsequent treatments are used after initial treatment based on the EAG's clinical expert's advice.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Patients staying on treatment longer with GPB 1% cream compared to oral antimuscarinics and botulinum toxin A.
- Patients spending less time on subsequent treatments for the remainder of their lives.
- Patients experiencing [redacted] compared to oral antimuscarinics.

Overall, the technology is modelled to affect costs by:

- Its lower cost per month compared to a basket of different oral antimuscarinics.
- Its delivery only in primary care compared to: oral antimuscarinics, which are given in both primary care and secondary care; and botulinum toxin A, which is only given in secondary care.
- Its lower cost of administration and monitoring compared to botulinum toxin A.
- Patients spending less time on subsequent treatments for the remainder of their lives.

The modelling assumptions that have the greatest effect on the ICER are:

- Source of utility values used for the Hyperhidrosis Disease Severity Scale (HDSS) health states.
- Separating the cost-effectiveness analysis results by primary care and secondary care settings.
- Reducing the time horizon of the model to two years.
- Removing the impact of [redacted] adverse events.
- Changing the rate of treatment discontinuation for oral antimuscarinics and botulinum toxin A.
- Including the HRQoL benefits of subsequent treatments.

1.3 EAG's key issues

Table 2 to

Table 15 present the EAG's key issues.

Table 2. Issue 1: Population in the Hyp-18/2016 Phase 3a and 3b trial does not align with the company's proposed positioning for GPB 1% cream

Report section	2.3.1 and 3.2
Description of issue and why the EAG has identified it as important	The EAG is concerned that the population in the key trial providing clinical evidence on GPB 1% cream (Hyp-18/2016 Phase 3a and 3b trial) does not align with the company's proposed positioning for GPB 1% cream in the NHS treatment pathway in terms of prior treatments. The company's proposed positioning for GPB 1% cream in the NHS is for use after lifestyle advice and topical aluminium chloride preparations, however, the inclusion criteria for the Hyp-18/2016 Phase 3a and 3b trials do not appear to specify any requirements regarding prior treatment with topical aluminium chloride preparations. In addition, based on data received in response to the clarification questions, it appears that fewer than 15% of patients in the Hyp-18/2016 Phase 3a and 3b trials had received at least 1 prior hyperhidrosis treatment. The EAG is, therefore, concerned about the generalisability of the results from the Hyp-18/2016 Phase 3a and 3b trial to the company's proposed positioning of GPB 1% cream in UK clinical practice (See Section 2.3). The EAG is particularly concerned that patients who have failed on first-line treatments may potentially be more challenging to treat and so may be less likely to respond to subsequent treatments. [redacted] In addition, these results are from the Phase 3a part of the trial whereas the Phase 3b data are used in the economic model. The EAG notes that subgroup results based on prior treatment status are not reported in the CS or CSR for the Hyp-18/2016 Phase 3b trial.
What alternative approach has the EAG suggested?	The EAG considers subgroup analysis for the Phase 3b patients based on prior treatments could be conducted and the results for the prior treatment subgroup utilised in a scenario analysis in the economic model.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers subgroup analysis for the Phase 3b patients based on prior treatments could be conducted and the results for the prior treatment subgroup utilised in a scenario analysis in the economic model.

Abbreviations: EAG, External Assessment Group; GPB, Glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, Incremental cost-effectiveness ratio; NHS, National Health Service; UK, United Kingdom.

Table 3. Issue 2: Cost-effectiveness analysis not stratified by primary care and secondary care setting

Report section	2.3.2 and 4.2.2.1
Description of issue and why the EAG has identified it as important	In Figure 2 of the CS, the proposed position of GPB 1% cream is: • As an alternative to oral anticholinergic medication (antimuscarinics) in primary care. • Prior to oral anticholinergic medication (antimuscarinics) and botulinum toxin type A in secondary care. However, the economic model does not make a distinction between healthcare settings, instead implementing proportions of the type of care setting used for administration and monitoring of patients on GPB 1% cream and the comparators. The company has assumed that GPB 1% cream is only administered in a primary care setting, which contradicts Figure 2 of the CS. The company explained that in the long-term, GPB 1% cream is expected to be used only in primary care as an alternative to anticholinergics. The company considered that there is a prevalent population in secondary care who would also be eligible for treatment with GPB 1% cream and have stated that they expect the cream to displace the use of oral antimuscarinics and botulinum toxin A in the future. Additionally, the company has used a concessionary price (£103.52) for propantheline bromide instead of the drug tariff price (£20.74), based on price data from January 2025 from Community Pharmacy England. The company's justification for using a concessionary price is that since February 2024, the price of propantheline bromide has been over £100 due to supply issues.
What alternative approach has the EAG suggested?	Given the company's proposed position of GPB 1% cream, the EAG recommended the company to provide two separate models to reflect the primary care and secondary care positions of GPB 1% cream, as the company's base case approach means that the fully incremental analysis is uninterpretable. Based on information from its clinical experts, the EAG considers that the main comparator for the primary care model would be propantheline bromide as it is the only treatment with marketing authorisation for PAHH and would be predominantly prescribed by GPs. Additionally, the EAG considers that it is inappropriate to use a concessionary price for propantheline bromide in the model. The NICE manual states that "*for medicines that are mainly prescribed in primary care, base prices on the drugs tariff*". The EAG notes that based on open prescribing data, from 2010 to Feb 2024, the price has been stable at £20.74 or just below. As such, the EAG considers that the drug tariff price is the typical price for propantheline bromide and that a short-term concessionary price should not be used to inform decision making.

	For the secondary care model, the EAG's clinical expert considers that the comparators would be modified-release oxybutynin 5mg once daily and botulinum toxin A. The company supplied scenario analyses reflecting a primary care and secondary care setting, but did not include this as part of their base case.
What is the expected effect on the cost-effectiveness estimates?	Using the corrected company base case, the ICER remained dominant for the comparison with propantheline bromide in the primary care model and from [redacted] to [redacted] for the comparison with modified-release oxybutynin in the secondary care model. For the comparison with botulinum toxin A in the secondary care model, the ICER remained dominant. When the drug tariff price for propantheline bromide is used in the primary care model, the corrected company ICER [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	The scenarios provided by the company resolve the issue.

Abbreviations: CS, company submission; EAG, External Assessment Group; GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; PAHH, primary axillary hyperhidrosis; QALY, quality-adjusted life-year.

Table 4. Issue 3: Lack of correlation between sweat production and HDSS score

Report section	3.3.2
Description of issue and why the EAG has identified it as important	The EAG considers that there appears to be a lack of correlation between sweat production and HDSS scores with GPB 1% cream in the Hyp-18/2016 Phase 3b newly recruited patients. The EAG considers this to be of particular concern given the subjective nature of HDSS and the open-label design of the study, and [redacted] The EAG considers this to be particularly concerning given Issue 1, where the EAG considers that [redacted], based on their proposed positioning of GPB 1% cream. The EAG notes that absolute change in total sweat production assessed by gravimetry was the primary efficacy endpoint in Hyp-18/2016 Phase 3a, and also in Phase 3b newly recruited patients, and that this is an objective measure. The EAG also notes that absolute reduction in sweat production from baseline to day 29 for Hyp-18/2016 Phase 3a FASa in logarithmic values was [redacted]). However, the EAG is concerned that HDSS score is the key clinical effectiveness measure used within the company's economic model.
What alternative approach has the EAG suggested?	The EAG considers this to be an unresolvable limitation of the data available for GPB 1% cream (beyond what is outlined in Issue 1). The use of an objective measure such as sweat production and/or a composite outcome (e.g. sweat production + HDSS) could be explored in scenario analyses within the economic model.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Scenario analyses using an objective measure such as sweat production and/or a composite outcome (e.g. sweat production + HDSS) in scenario analyses within the economic model.

Abbreviations: EAG, External Assessment Group; GPB, Glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, Incremental cost-effectiveness ratio; NHS, National Health Service; UK, United Kingdom.

Table 5. Issue 4: Uncertainty in the indirect treatment comparisons

Report section	3.4
Description of issue and why the EAG has identified it as important	The company conducted Bucher ITCs for antimuscarinics and botulinum toxin A versus GPB 1% cream. The EAG has concerns about the reliability and generalisability of the results from these analyses. The EAG is concerned about the differences between the study populations and the timepoints at which outcomes were measured for the comparison of GPB 1% cream with antimuscarinics. As noted by the company, these discrepancies likely violate the assumptions required for the Bucher method to produce reliable results and contribute to the uncertainty in the estimated treatment effects. With regards the Lowe *et al.* 2007 data for botulinum toxin A in the ITCs, the EAG is concerned that the data are from only a single timepoint of 4 weeks and, therefore, do not reflect the expected treatment waning with botulinum toxin A reported by the EAG's clinical expert from approximately month 4 onwards. In addition, the EAG notes that the ORs are [redacted]. The EAG, thus, considers the results of the ITCs for GPB 1% cream versus botulinum toxin A to be subject to [redacted]. The EAG notes that the Wade *et al.* NMA was used in a scenario analysis within the company's economic model but considers this also to have limitations due to differences in the treatments included in the antimuscarinics studies, and differences in the populations and timing of outcome assessment in the botulinum toxin A studies.
What alternative approach has the EAG suggested?	The EAG considers that the use of alternative, more complex, indirect treatment comparison methods could potentially help to resolve some of the underlying differences between the trial populations in the comparator studies and the GPB 1% cream trial. However, the trial population for antimuscarinics does not fully align with the marketing authorisation population for GPB 1% cream in terms of patients with severe primary axillary hyperhidrosis (PAHH). In addition, the prior treatments in the botulinum toxin A trial are not fully reflective of UK clinical practice and the company's proposed positioning of GPB 1% cream. The EAG therefore also considers that further indirect treatment comparisons would only partially address the current uncertainties in the clinical evidence.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers this to be an unresolvable limitation based on the currently available clinical evidence but considers that the use of alternative more complex indirect treatment comparison methods could potentially help to resolve some of the underlying differences between the trial populations in the comparator studies and the GPB 1% cream trial.

Abbreviations: EAG, External Assessment Group; GPB, Glycopyrronium bromide; NMA, network meta-analysis; UK, United Kingdom.

Table 6. Issue 5: Utility values used for the HDSS health states

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	The company's base case utility values for the HDSS health states are based on EQ-5D-5L values obtained from a published thesis, which has also been used to inform other published cost-effectiveness analyses. The NICE reference case stipulates a preference for EQ-5D-3L values, measured directly by patients. Additionally, it is unclear if the UK or the USA value set has been used for the utility values. Additionally, EQ-5D data have been collected from both USA and UK patients.
What alternative approach has the EAG suggested?	In the Hyp1-18/2016 Phase 3b trial, EQ-5D data were not collected and instead quality of life was measured using the DLQI. A mapping algorithm for DLQI to EQ-5D exists. During clarification, the EAG requested that the company undertake a mapping analysis to estimate utility values, which would adhere to the NICE reference case. The company declined to conduct this analysis. Summary score EQ-5D-5L values can be mapped to EQ-5D-3L using the published calculator from Hernandez Alava *et al*. 2020. The EAG mapped the company's base case utility values to the EQ-5D-3L but considers the values were relatively low when compared to other disease areas, such as multiple myeloma and potentially lack face validity. As such, the EAG considers its alternative values are not appropriate for an EAG base case and has been unable to produce a preferred base case. Instead, scenarios using its preferred assumptions and exploring the company's base case utility values and its alternative mapped EQ-5D-3L values are presented.
What is the expected effect on the cost-effectiveness estimates?	Using the corrected company base case and analyses separated by care setting (see Key Issue 2), the ICER remained dominant for the comparison with propantheline bromide in the primary care model but the QALY gain [redacted] from [redacted] to [redacted]. The ICER [redacted] from [redacted] to [redacted] for the comparison with modified-release oxybutynin in the secondary care model. For the comparison with botulinum toxin A in the secondary care model, the ICER remained dominant, but the QALY gain [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	Utility values for the HDSS health states based on a mapped analysis of DLQI values to EQ-5D-3L values.

Abbreviations: DLQI, Dermatology Life Quality Index; EAG, External Assessment Group; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Table 7. Issue 6: Lifetime horizon of the economic model is potentially too long

Report section	4.2.2.1
Description of issue and why the EAG has identified it as important	The EAG considers that the model's lifetime horizon may be excessive, given the nature of the condition and the treatments under consideration. In the NICE manual, it states, "*a time horizon shorter than a patient's lifetime could be justified if there is no differential mortality effect between technologies and the differences in costs and clinical outcomes relate to a relatively short period*". For the company's base case, no difference in mortality is assumed. Additionally, after week 72, the company assumed that there are no further transitions between HDSS health states for GPB 1% cream and oral antimuscarinics. For botulinum toxin A, every 6 months, patients return to baseline HDSS scores as part of the company's treatment effect waning assumptions. As such, the majority of the modelled treatment effectiveness in the model is based on assumptions. Furthermore, patients spend the majority of the model's time horizon in the subsequent treatment health state. Patients on GPB 1% cream spend approximately [redacted] years out the 65 years of the model time horizon in the subsequent treatment health state. For patients in the comparator arms of the model, approximately [redacted] years are spent in the subsequent treatment health state. With regards to costs and clinical outcomes, the EAG's clinical expert advised that treatment response typically becomes clear within the first month, allowing non-responders to quickly transition to alternative therapies. Furthermore, the EAG's clinical expert considered that within two years, most patients are expected to have identified an effective treatment and are likely to remain on it long-term
What alternative approach has the EAG suggested?	The EAG prefers a shorter time horizon of two years is used for the cost-effectiveness analysis.
What is the expected effect on the cost-effectiveness estimates?	Using the corrected company base case, the ICER remained dominant for the comparison with propantheline bromide in the primary care model. The QALY gain [redacted]. For the comparison with modified-release oxybutynin in the secondary care model the ICER remained dominant, but the QALY gain [redacted]. For the comparison with botulinum toxin A in the secondary care model, the ICER remained dominant, but the QALY gain [redacted].
What additional evidence or analyses might help to resolve this key issue?	The EAG scenario resolves the issue.

Abbreviations: EAG, External Assessment Group; GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Table 8. Issue 7: Assumptions around treatment waning for botulinum toxin A

Report section	4.2.3.3
Description of issue and why the EAG has identified it as important	In the company's model, from week 4 to week 26, the treatment effect for botulinum toxin A wanes linearly until patients return to their baseline HDSS score. The EAG's clinical expert advised that botulinum toxin A is one of the most effective treatments for severe PAHH and that patients would see a clinically significant reduction in sweating and improvement in quality of life within one week of treatment and this would be maintained up to month 4. The EAG's clinical expert considered that the company's base case assumption of treatment waning from week 4 for botulinum toxin A was clinically implausible.
What alternative approach has the EAG suggested?	In their clarification response, the company provided a scenario where the treatment effectiveness of botulinum toxin A wanes after week 16 until week 26 (next administration of botulinum toxin A). The EAG considers that the company's scenario is a more clinically plausible assumption of treatment waning for botulinum toxin A.
What is the expected effect on the cost-effectiveness estimates?	For the comparison with botulinum toxin A in the secondary care model, the ICER remained dominant, but the QALY gain [redacted].
What additional evidence or analyses might help to resolve this key issue?	The company's scenario resolves the issue.

Abbreviations: EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; PAHH, primary axillary hyperhidrosis; QALY, quality-adjusted life-year.

Table 9. Issue 8: Inclusion of the impact of adverse events on costs and QALYs

Report section	4.2.5.1
Description of issue and why the EAG has identified it as important	[redacted] or the comparator studies. The EAG's clinical expert advised that the AEs included in the economic model would not be severe enough to be treated. Instead, via patient monitoring, AEs would be managed through dose reductions or treatment discontinuation. Both patient monitoring and treatment discontinuation are already included in the model. Typically, for cost-effectiveness analyses, only AEs that have a significant cost and HRQoL burden are considered in the economic model.
What alternative approach has the EAG suggested?	The EAG considers the company's reason for keeping the impact of AEs in the model is not sufficiently justified and so ran a scenario excluding AEs from the model.
What is the expected effect on the cost-effectiveness estimates?	Using the corrected company base case, the ICER remained dominant for the comparison with propantheline bromide in the primary care model but [redacted]. The ICER [redacted] from [redacted] to [redacted] for the comparison with modified-release oxybutynin in the secondary care model. For the comparison with botulinum toxin A in the secondary care model, the ICER remained dominant, but the [redacted].
What additional evidence or analyses might help to resolve this key issue?	The scenario resolves the issue

Abbreviations: AE, adverse event; EAG, External Assessment Group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Table 10. Issue 9: Monitoring costs of oral antimuscarinics

Report section	4.2.7.4
Description of issue and why the EAG has identified it as important	The company applied administration and monitoring costs for all treatments, based on an assumed healthcare setting (i.e. primary care or secondary care). For all treatments, the company assumed that patients are monitored on a quarterly basis in the first year, followed by annual monitoring thereafter. However, the EAG's clinical expert advised that patients, (except those on botulinum toxin A) will be monitored annually in the first year of treatment. The company stated that all administration and monitoring for patients receiving GPB 1% cream will be undertaken in primary care. The company stated that GPs are encouraged to use the advice and guidance (A&G) scheme to access advice from hospital specialists and that the management of severe PAHH is an area where this would be used to encourage management in primary care rather than referrals to secondary care. The company noted that the use of A&G services would be most applicable to treatment with antimuscarinics due to associated side effects. For oral antimuscarinics, the company model assumes that 25% are administered through A&G services and the cost of A&G services is applied at every monitoring appointment. The EAG's clinical experts highlighted that use of A&G services would only happen once to support diagnosis and treatment of a patient and that ongoing support would not be provided. Additionally, they advised that very few hyperhidrosis patients are seen through A&G services (10%).
What alternative approach has the EAG suggested?	The EAG does not consider applying A&G costs beyond the initial appointment to be appropriate. The EAG explored a scenario using the primary care model in which the additional cost of A&G services is only applied to the first appointment for 10% of primary care patients in the antimuscarinics arm. Additionally, the EAG ran a scenario that includes an assumption of annual monitoring for patients on GPB 1% cream and antimuscarinics with the appointments taking place in primary care, affecting both the primary care and secondary care model.
What is the expected effect on the cost-effectiveness estimates?	For the primary care model, the EAG's scenarios had minimal impact on the ICER. For the secondary care model, the assumption of annual monitoring taking place in primary care [redacted] the ICER from [redacted] to [redacted] for the comparison with modified-release oxybutynin. For the comparison with botulinum toxin A, the ICER remained dominant.
What additional evidence or analyses might help to resolve this key issue?	The EAG scenarios resolve the issues.

Abbreviations: A&G, advice and guidance; EAG, External Assessment Group; GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; PAHH, primary axillary hyperhidrosis; QALY, quality-adjusted life-year.

Table 11. Issue 10: Monitoring costs of botulinum toxin A

Report section	4.2.7.4
Description of issue and why the EAG has identified it as important	In the company's model, all botulinum toxin A administration is undertaken in secondary care and is given every six months. The company applied administration costs related to botulinum toxin A administration based on assumptions made in Wade *et al*.2017 which assumed 45 minutes of nurse time (£35.25) plus the NHS reference cost for intermediate skin procedures, general surgery (£156). In addition to the administration costs for botulinum toxin A, the company also applied a separate monitoring cost equivalent to that used for secondary care outpatient appointments for patients receiving antimuscarinics, applied quarterly in the first year and annually thereafter. The EAG was concerned that the administration and monitoring costs for botulinum toxin A were overestimated. The EAG's clinical expert stated that the time taken to review a patient and deliver treatment with botulinum toxin A would be around 20 minutes and conducted by a nurse. Additionally, the EAG's clinical expert explained that botulinum toxin A patients would be monitored as part of their next scheduled treatment appointment. An NHS protocol for botulinum toxin A for the treatment of PAHH specifically states that the appointment will last around 45 minutes with botulinum toxin A, administration under each arm taking around 15 to 20 minutes. It also states that patients can go home straight after treatment and therefore no post-procedure observation is required. Two other patient information sheets for botulinum toxin A for hyperhidrosis from other NHS trusts suggest a treatment time of 20 minutes to one hour, with the first administration given by a consultant.
What alternative approach has the EAG suggested?	The EAG ran a scenario where the first administration of botulinum toxin A is given by a consultant and only the cost of nurse time for a 45-minute appointment is applied thereafter (excludes the NHS reference cost). Additionally, in the EAG scenario, additional monitoring costs are removed as patients are assumed to be monitored as part of their next scheduled treatment appointment.
What is the expected effect on the cost-effectiveness estimates?	Using the corrected company base case, the ICER remained dominant for the comparison with propantheline bromide in the primary care model and changed from [redacted] to [redacted] for the comparison with modified-release oxybutynin in the secondary care model. For the comparison with botulinum toxin A in the secondary care model, the ICER remained dominant, but the [redacted].
What additional evidence or analyses might help to resolve this key issue?	The EAG scenario resolves the issue.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; PAHH, primary axillary hyperhidrosis; QALY, quality-adjusted life-year.

Table 12. Issue 11: Treatment discontinuation of oral antimuscarinics

Report section	4.2.7.6
Description of issue and why the EAG has identified it as important	The company base case results are driven by how quickly patients discontinue use of comparator treatments and move on to subsequent treatment, where patients experience no benefits of treatment (and return to baseline HDSS scores) but incur costs. The results of the ITC demonstrated that both oral antimuscarinics and botulinum toxin A are [redacted] However, the company's base case model results demonstrate that patients treated with GPB 1% cream are likely to experience a QALY gain of [redacted] compared to being treated with oral antimuscarinics. The EAG considers that it is [redacted] In the model, the per-cycle probability of discontinuing treatment with GPB 1% cream was [redacted]% compared to 5.3% for oral antimuscarinics, applied for the entire time horizon of the model (65 years). The EAG's clinical expert considered that most treatment discontinuations for oral antimuscarinics occur in the first month of treatment, and around one third of patients stop taking treatment. After the first month, the remaining patients are assumed to have a good response and tolerance to treatment and the overall discontinuation rate going forward is around 10%. Additionally, the EAG's clinical expert advised that within two years, most patients are expected to have identified an effective treatment and are likely to remain on it long-term.
What alternative approach has the EAG suggested?	Assuming a time horizon of two years based on the EAG's clinical expert view, the EAG calculated that the 2-week instantaneous rate of discontinuation is 0.20% for oral antimuscarinics after week 4. As such, the overall discontinuation rate, based on the EAG's clinical expert view is 43%, which is less than that used for the company's base case (50.9% overall, 5.3% per 2-week cycle), but the implementation of having a higher discontinuation rate early in the model, with a slower rate for the remainder of the model has a substantial impact on the cost-effectiveness results.
What is the expected effect on the cost-effectiveness estimates?	The EAG considers that assumptions made around the treatment discontinuation rate for oral antimuscarinics a primary driver of cost-effectiveness in the model. **Lifetime horizon**: Using the corrected company base case, the ICER [redacted] from [redacted] to [redacted] for the comparison with propantheline bromide in the primary care model and from [redacted] to [redacted] for the comparison with modified-release oxybutynin in the secondary care model. For the comparison with botulinum toxin A in the secondary care model, the ICER remained dominant.

	2-year time horizon: Using the corrected company base case, the ICER [redacted] from [redacted] to [redacted] for the comparison with propantheline bromide in the primary care model and from [redacted] to [redacted] for the comparison with modified-release oxybutynin in the secondary care model. For the comparison with botulinum toxin A in the secondary care model, the ICER remained dominant, but the QALY gain [redacted], driven by the reduction in the time horizon.
What additional evidence or analyses might help to resolve this key issue?	The scenario resolves the issue.

Abbreviations: EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 13. Issue 12: Treatment discontinuation of botulinum toxin A

Report section	4.2.7.6
Description of issue and why the EAG has identified it as important	The company base case results are driven by how quickly patients discontinue use of comparator treatments and move on to subsequent treatment, where patients experience no benefits of treatment (and return to baseline HDSS scores) but incur costs. The results of the ITC demonstrated that both oral antimuscarinics and botulinum toxin A are [redacted] However, the company's base case results demonstrate that patients treated with GPB 1% cream are likely to experience a QALY gain of [redacted] compared to being treated botulinum toxin A. The EAG considers that it is [redacted] In the model, the per-cycle probability of discontinuing treatment with GPB 1% cream was [redacted]% compared to 2.9% for botulinum toxin A, applied for the entire model time horizon (65 years). The EAG's clinical expert considered that a two-weekly discontinuation rate for botulinum toxin A is not reflective of current practice. They considered that after the first treatment patients would be booked in for their second treatment and have their response to treatment assessed at that appointment (after 6 months). At the second injection appointment, the dose would be adjusted based on response. As such, discontinuation of treatment is only likely to happen at the third treatment, if patients aren't responding to botulinum toxin A. The EAG's clinical expert advice aligns with published data for botulinum toxin A.
What alternative approach has the EAG suggested?	The EAG's clinical expert advised that if patients have a good response to botulinum toxin A, most receive their next scheduled injections and can remain on treatment for many years. Therefore, the EAG considers it is more appropriate to apply botulinum toxin A treatment discontinuation in the model at the timepoint of each administration (every 6 months), using the discontinued data from Lowe *et al*. presented in Table 31 of the CS.
What is the expected effect on the cost-effectiveness estimates?	Using the corrected company base case, the ICER remained dominant for the comparison with propantheline bromide in the primary care model and [redacted] from [redacted] to [redacted] for the comparison with modified-release oxybutynin in the secondary care model. For the comparison with botulinum toxin A in the secondary care model, the ICER remained dominant, but the QALY gain [redacted].
What additional evidence or analyses might help to resolve this key issue?	The scenario resolves the issue.

Abbreviations: CS, company submission; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Table 14. Issue 13: Exclusion of QALY benefit of subsequent treatments

Report section	4.2.8.1
Description of issue and why the EAG has identified it as important	In the company's economic model, only the costs of subsequent treatment were included and not the benefits. Instead, the company assumed that patients returned to their baseline HDSS score and accrued the utility values associated with that health state. The company considered that if patients had failed second-line treatment, their underlying PAHH may be more difficult to treat and, as such, they are unlikely to experience the same level of benefit as patients who are treated earlier but are still likely to incur the full costs of subsequent treatment. However, the company has presented no evidence to substantiate their claims around the effectiveness and HRQoL benefit of subsequent treatment. The EAG considers that the company's approach to the modelling of subsequent treatments is fundamentally flawed, as costs and benefits that are not aligned. This is a particular problem as both oral antimuscarinics and botulinum toxin A were found to be [redacted] but are assumed by the company to have a higher discontinuation rate than GPB 1% cream. The company's base case approach is biased against the comparators as the company's model estimates that most patients transition to subsequent treatment after [redacted] months for antimuscarinics and [redacted] years for botulinum toxin A and then spend approximately [redacted] years in the subsequent treatment health state only accruing the utility value associated with their baseline HDSS score. Patients on GPB 1% cream move to subsequent treatment after [redacted] years and spend approximately [redacted] years in the subsequent treatment health state.
What alternative approach has the EAG suggested?	The company explored a scenario that estimated a treatment-specific weighted average utility for the subsequent treatment health state, which the EAG considers is a more appropriate assumption compared to their base case approach. The EAG considers including the 2-year time horizon (Key issue 6) is useful to include for the scenario.
What is the expected effect on the cost-effectiveness estimates?	The EAG considers that the lack of benefit of subsequent treatment is a key driver of cost-effectiveness in the model. **Company base case utility values, 2-year time horizon:** Using the corrected company base case, the ICER [redacted] to [redacted] for the comparison with propantheline bromide in the primary care model and from [redacted] to [redacted] for the comparison with modified-release oxybutynin in the secondary care model. For both the scenarios of GPB 1% cream versus antimuscarinics, the incremental QALYs [redacted]. For the comparison with botulinum toxin A in the secondary care model, the ICER changed from dominant to [redacted], and the incremental QALYs [redacted].

	EAG alternative utility values, 2-year time horizon: Using the corrected company base case, the ICER [redacted] to [redacted] for the comparison with propantheline bromide in the primary care model and from [redacted] to [redacted] for the comparison with modified-release oxybutynin in the secondary care model. For the comparison with botulinum toxin A in the secondary care model, the ICER changed from dominant to [redacted].
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that the subsequent treatment health state could have been modelled in the same way as an initial treatment, i.e. based on the four HDSS health states and that it would have been a more accurate way to capture the subsequent treatment costs and benefits. However, the EAG considers that the company's assumption of a treatment-specific average weighted utility value for the subsequent treatment health state provides an estimation of the impact of including benefits of subsequent treatment for committee to consider.

Abbreviations: EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; PAHH, primary axillary hyperhidrosis; QALY, quality-adjusted life-year; SW, south-west.

Table 15. Issue 14: Basket of subsequent treatments

Report section	4.2.8.1
Description of issue and why the EAG has identified it as important	The EAG's clinical expert validated the company's basket of subsequent treatments dependent on initial treatment and considered that the company's assumption of subsequent treatments did not reflect current clinical practice. Instead, they provided an alternative view of subsequent treatments in secondary care, which included a proportion of patients who do not receive further NHS care and instead are privately treated or do not access any further treatments at all. As described in Issue 4, the EAG prefers the cost-effectiveness analysis to be separated and based on care setting, as such the EAG's clinical expert's estimates of subsequent treatments are based on patients receiving their initial treatment in primary care and secondary care. Please refer to Section 4.2.8 for data on the basket of subsequent treatments assumed by the company and by the EAG.
What alternative approach has the EAG suggested?	The company supplied a scenario for implementing the EAG's clinical expert proportions of subsequent treatment that is only applicable to the secondary care model. The company combined this scenario with the scenario implementing a treatment-specific average weighted HDSS score for the subsequent treatment health state. For patients who receive no further NHS treatment and do seek private treatment, they revert back to their baseline HDSS scores. The EAG ran a scenario implementing the EAG's clinical experts view on subsequent treatment for patients in the primary care model, including the treatment-specific average weighted HDSS score for the subsequent treatment health state. The EAG considers including the 2-year time horizon (Key issue 6) is useful to include for both scenarios.
What is the expected effect on the cost-effectiveness estimates?	**Company base case utility values, 2-year time horizon:** Using the corrected company base case, the ICER [redacted] to [redacted] for the comparison with propantheline bromide in the primary care model and from [redacted] to [redacted] for the comparison with modified-release oxybutynin in the secondary care model. For both the scenarios of GPB 1% cream versus antimuscarinics, the incremental QALYs [redacted]. For the comparison with botulinum toxin A in the secondary care model, the ICER remained dominant, but the QALY gain [redacted]. **EAG alternative utility values, 2-year time horizon**:

	Using the corrected company base case, the ICER [redacted] to [redacted] for the comparison with propantheline bromide in the primary care model and from [redacted] to [redacted] for the comparison with modified-release oxybutynin in the secondary care model. For the comparison with botulinum toxin A in the secondary care model, the ICER remained dominant, but the QALY gain [redacted].
What additional evidence or analyses might help to resolve this key issue?	The scenario resolves the issue.

Abbreviations: EAG, External Assessment Group; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SW, south-west.

1.4 Secondary issues identified by the EAG

The EAG identified some secondary issues that had minimal impact on the ICER but were considered to be more appropriate than the company's base case approach. These are as follows:

- Use of the ONS life tables from 2017-2019, as per guidance in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 23.
- Botulinum toxin A odds ratio (OR) for ≥1-point improvement in the HDSS score assumed to be the same as that for ≥2-point improvement.

1.5 Company's modelling errors identified by the EAG

The EAG corrected the company's base case to take into account updated prices for oxybutynin and oral glycopyrronium bromide and corrected two errors in the model. Further details of the updates and corrections made to the company base case are presented in Section 5.2.1. As a result of the corrections, the ICERs for GPB 1% cream versus oral antimuscarinics and botulinum toxin A remained dominant.

1.6 Summary of EAG's preferred assumptions and resulting ICER

As discussed in Key issue 4, the EAG does not consider either the company's base case EQ-5D-5L utility values or the EAG's estimated EQ-5D-5L values mapped to EQ-5D-3L to be appropriate for an EAG base-case analysis. Furthermore, the EAG is not aware of any alternative EQ-5D-3L values related to HDSS score in the existing literature. Consequently, due to the absence of appropriate utility values, the EAG is unable to propose a preferred base-case analysis. Instead, the EAG presents two scenario options that use the company's base case utility values and the EAG's alternative mapped utility values in addition to the EAG's other preferred model assumptions. As mentioned in Key issue 5, the company's proposed position in the treatment pathway for GPB 1% cream is in both primary and secondary care and as such the EAG has created two separate sets of preferred assumptions based on care setting.

In summary, the EAG has provided the following scenarios in lieu of an EAG base case:

- Primary care model using the company's base case EQ-5D-5L utility values and the EAG's other preferred model assumptions (Table 16 and Table 17).
- Secondary care model using the company's base case EQ-5D-5L utility values and the EAG's other preferred model assumptions (Table 18 and Table 19).

- Primary care model using the EAG's alternative EQ-5D-3L mapped utility values and the EAG's other preferred model assumptions (Table 20 to Table 23).
- Secondary care model using the EAG's alternative EQ-5D-3L mapped utility values and the EAG's other preferred model assumptions (Table 24 to Table 27).

Table 16. Primary care model: Deterministic results using the EAG's preferred model assumptions and the company's base case utility values – GPB 1% cream versus propantheline bromide

Preferred assumption	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Company base case	[redacted]	[redacted]	Dominant
Corrected company base case	[redacted]	[redacted]	Dominant
Comparator is propantheline bromide	[redacted]	[redacted]	Dominant
Price of propantheline bromide set to £20.74	[redacted]	[redacted]	[redacted]
2-year time horizon	[redacted]	[redacted]	Dominant
Treatment effectiveness of botulinum toxin A wanes after week 16	[redacted]	[redacted]	Dominant
Botulinum toxin A OR for ≥1-point improvement in the HDSS score assumed to be the same as that for ≥2-point improvement	[redacted]	[redacted]	Dominant
ONS lifetables from 2017-2019	[redacted]	[redacted]	Dominant
Removal of AEs	[redacted]	[redacted]	Dominant
Administration costs for propantheline bromide: 90% primary care, 10% primary care + A&G services (1st appointment only)	[redacted]	[redacted]	Dominant
Apply consultant cost for first botulinum toxin A administration and nurse 45 minutes for subsequent	[redacted]	[redacted]	Dominant
Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care	[redacted]	[redacted]	Dominant
EAG discontinuation rate for antimuscarinics	[redacted]	[redacted]	[redacted]
Botulinum toxin A discontinuation rate applied to each administration and only using Lowe *et al*. 2007 discontinuation data.	[redacted]	[redacted]	[redacted]
EAG expert view on basket of subsequent treatment	[redacted]	[redacted]	[redacted]
Average weighted utility value for subsequent treatment health state	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 17. Primary care model - EAG scenario using preferred model assumptions and the company's base case utility values – GPB 1% cream versus propantheline bromide

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Propantheline bromide	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Propantheline bromide	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 18. Primary care model: Deterministic results using the EAG's preferred model assumptions and the company's base case utility values – GPB 1% cream versus propantheline bromide

Preferred assumption	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Company base case	[redacted]	[redacted]	Dominant
Corrected company base case	[redacted]	[redacted]	Dominant
Comparator is propantheline bromide	[redacted]	[redacted]	Dominant
Price of propantheline bromide set to £20.74	[redacted]	[redacted]	[redacted]
2-year time horizon	[redacted]	[redacted]	Dominant
Treatment effectiveness of botulinum toxin A wanes after week 16	[redacted]	[redacted]	Dominant
Botulinum toxin A OR for ≥1-point improvement in the HDSS score assumed to be the same as that for ≥2-point improvement	[redacted]	[redacted]	Dominant
ONS lifetables from 2017-2019	[redacted]	[redacted]	Dominant
Removal of AEs	[redacted]	[redacted]	Dominant
Administration costs for propantheline bromide: 90% primary care, 10% primary care + A&G services (1st appointment only)	[redacted]	[redacted]	Dominant
Apply consultant cost for first botulinum toxin A administration and nurse 45 minutes for subsequent	[redacted]	[redacted]	Dominant
Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care	[redacted]	[redacted]	Dominant
EAG discontinuation rate for antimuscarinics	[redacted]	[redacted]	[redacted]

Preferred assumption	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Botulinum toxin A discontinuation rate applied to each administration and only using Lowe *et al*. 2007 discontinuation data.	[redacted]	[redacted]	[redacted]
EAG expert view on basket of subsequent treatment	[redacted]	[redacted]	[redacted]
Average weighted utility value for subsequent treatment health state	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 19. Primary care model - EAG scenario using preferred model assumptions and the company's base case utility values – GPB 1% cream versus propantheline bromide

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Propantheline bromide	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Propantheline bromide	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 20. Secondary care model: Deterministic results using the EAG's preferred model assumptions and the company's base case utility values

Preferred assumption	Vs. modified release oxybutynin			Vs. botulinum toxin A		
	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Company base case	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Corrected company base case	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Comparators are modified-release oxybutynin 5 mg and botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
2-year time horizon	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Treatment effectiveness of botulinum toxin A wanes after week 16	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Botulinum toxin A OR for ≥1-point improvement in the HDSS score assumed to be the same as that for ≥2-point improvement	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
ONS lifetables from 2017-2019	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Removal of AEs	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Apply consultant cost for first botulinum toxin A administration and nurse 45 minutes for subsequent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
EAG discontinuation rate for antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Botulinum toxin A discontinuation rate applied to each administration and only using Lowe *et al*. 2007 discontinuation data.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG expert view on basket of subsequent treatment and average weighted utility value for subsequent treatment health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred assumption	Vs. modified release oxybutynin			Vs. botulinum toxin A		
	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 21. Secondary care model - EAG scenario using preferred model assumptions and the company's base case utility values – GPB 1% cream versus modified-release oxybutynin

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Modified-release oxybutynin	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Modified-release oxybutynin	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 22. Secondary care model - EAG scenario using preferred model assumptions and the company's base case utility values – GPB 1% cream versus botulinum toxin A

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 23. Fully incremental analysis (based on PSA results) – secondary care model, company's base case utility values

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
GPB 1% cream	[redacted]	[redacted]	[redacted]	-	-	-	-
Modified-release oxybutynin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 24. Secondary care model: Deterministic results using the EAG's preferred model assumptions and the EAG's alternative utility values

Preferred assumption	Vs. modified release oxybutynin			Vs. botulinum toxin A		
	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Company base case	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Corrected company base case	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Comparators are modified-release oxybutynin 5 mg and botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
2-year time horizon	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Treatment effectiveness of botulinum toxin A wanes after week 16	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Botulinum toxin A OR for ≥1-point improvement in the HDSS score assumed to be the same as that for ≥2-point improvement	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
ONS lifetables from 2017-2019	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Removal of AEs	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Apply consultant cost for first botulinum toxin A administration and nurse 45 minutes for subsequent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
EAG discontinuation rate for antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Botulinum toxin A discontinuation rate applied to each administration and only using Lowe *et al*. 2007 discontinuation data.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred assumption	Vs. modified release oxybutynin			Vs. botulinum toxin A		
	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
EAG expert view on basket of subsequent treatment and average weighted utility value for subsequent treatment health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 25. Secondary care model - EAG scenario using preferred model assumptions and the EAG's alternative utility values – GPB 1% cream versus modified-release oxybutynin

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Modified-release oxybutynin	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Modified-release oxybutynin	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 26. Secondary care model - EAG scenario using preferred model assumptions and the EAG's alternative utility values – GPB 1% cream versus botulinum toxin A

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 27. Fully incremental analysis (based on PSA results) – secondary care model, EAG alternative utility values

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
GPB 1% cream	[redacted]	[redacted]	[redacted]	-	-	-	-

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Modified-release oxybutynin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

1.7 Outline of confidential comparator or subsequent treatment prices

A confidential price is available for botulinum toxin A and so the EAG has produced a confidential appendix to this report. Further details of the confidential appendix are presented in Section 5.4.

2 Background

This report contains the External Assessment Group (EAG)'s critique of the clinical and cost-effectiveness evidence submitted for the Single Technology Appraisal (STA) of glycopyrronium bromide 1% cream (Axhidrox®, Leith Healthcare) for treating severe primary axillary hyperhidrosis (PAHH). The company received UK marketing authorisation from the MHRA in June 2025[1] for glycopyrronium bromide 1% cream (GPB 1% cream) in this indication in June 2025 as follows: GPB 1% cream for the topical treatment of severe primary axillary hyperhidrosis in adults. In addition, the company reported that GPB 1% cream has marketing authorisation for the topical treatment of severe PAHH in adults in 23 Member States of the European Economic area.

2.1 Critique of the company's description of underlying health problem

Within Section 1 of the company submission (CS), the company provides an overview of:

- GPB 1% cream, including its mechanism of action, indications, dose and method of administration (Section 1.1 of the CS);
- Hyperhidrosis, particularly PAHH, including diagnosis and classification, its impact on patient quality of life, and the current treatment pathway (Section 1.2 of the CS).

Hyperhidrosis is estimated to affect at least 1% of the population but the true prevalence could be greater as it is thought that many patients do not seek medical treatment.[2] Hyperhidrosis is characterised by excessive sweating[3] and PAHH is a localised form of hyperhidrosis affecting the axillae. The hyperhidrosis disease severity scale (HDSS) is a validated tool for the assessment of hyperhidrosis, with a score of 3 or 4 classed as severe disease.[4, 5]

2.2 Critique of the company's overview of current service provision

The company's overview of the current treatment pathway for PAHH is summarised in Figure 1. The EAG notes that the NICE Clinical Knowledge Summaries (CKS) recommendations for hyperhidrosis include that patients receive lifestyle advice and try topical 20% aluminium chloride hexahydrate preparations, such as roll-on antiperspirants and sprays, that are available over-the-counter as part of the first-line treatment for PAHH.[6] Clinical expert advice to the EAG also suggested that this is consistent with UK clinical practice.

The EAG notes that the NICE CKS recommendations for management of hyperhidrosis in patients who do not respond to, or are intolerant of, topical treatments and self-care measures, include referral to specialist care (e.g. secondary care). The EAG also notes that the company's treatment

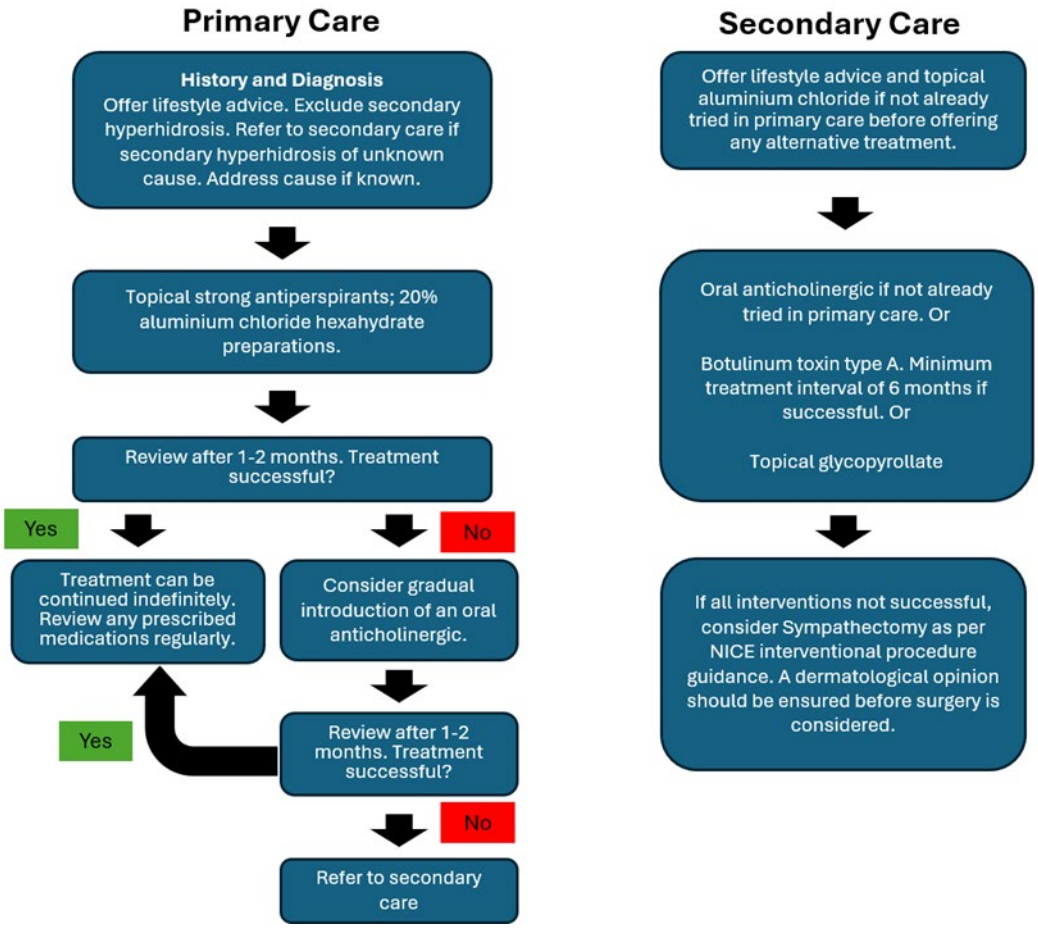
pathway includes 'consider gradual introduction of an oral anticholinergic' as a treatment in primary care. Both the company and the EAG clinical expert advice suggest that while oral anticholinergics may be commenced in primary care, they are not consistently offered as a treatment option by all primary care providers. In terms of secondary care treatments, the EAG's clinical expert reported that treatment options vary by centre, with not all centres able to provide botulinum toxin type A (hereafter referred to as botulinum toxin A) and availability of the different oral anticholinergics varying too. The only oral anticholinergic with UK marketing authorisation for hyperhidrosis is propantheline bromide but other oral anticholinergics are used "off-label"; these include oxybutynin and glycopyrronium bromide. In the CS the company reported that some primary care providers can only prescribe the oral anticholinergic with marketing authorisation, propantheline bromide.

The EAG's clinical expert reported that the oral anticholinergic oxybutynin is available in both a standard dose format and a modified release formulation, although neither are licensed for use in hyperhidrosis. The EAG's clinical expert stated that modified release oxybutynin is generally the preferred first oral anticholinergic in their clinical practice for PAHH (secondary care) but also highlighted that usage of other oral anticholinergics maybe preferred in other centres, particularly propantheline bromide given its marketing authorisation. The EAG's clinical expert also considered oral glycopyrronium bromide to be rarely used in UK clinical practice for PAHH and the EAG notes that it is associated with higher costs compared with propantheline bromide and oxybutynin (see Section 4.2.7.1).

The EAG notes that the company included topical glycopyrrolate as a secondary care treatment option in Figure 1. However, it was also reported in the CS that glycopyrronium bromide (glycopyrrolate) 2% w/w in cetomacrogol cream is rarely used for PAHH and that it does not have marketing authorisation for use in PAHH. In addition, the EAG's clinical expert reported that surgery is rarely used for PAHH and the EAG notes that this is consistent with information in the British Association of Dermatologists guidance for hyperhidrosis, where it is stated that "surgical approaches are rarely utilised due to the potential risks involved".[7]

The EAG's clinical expert reported that iontophoresis is a further hyperhidrosis treatment option that may be available in secondary care, but its availability for PAHH in the UK NHS is limited.

Figure 1. Current care pathway for PAHH (reproduced from Figure 1 of the CS)



Abbreviations: NICE, National Institute for Health and Care Excellence; PAHH, Primary Axillary Hyperhidrosis.

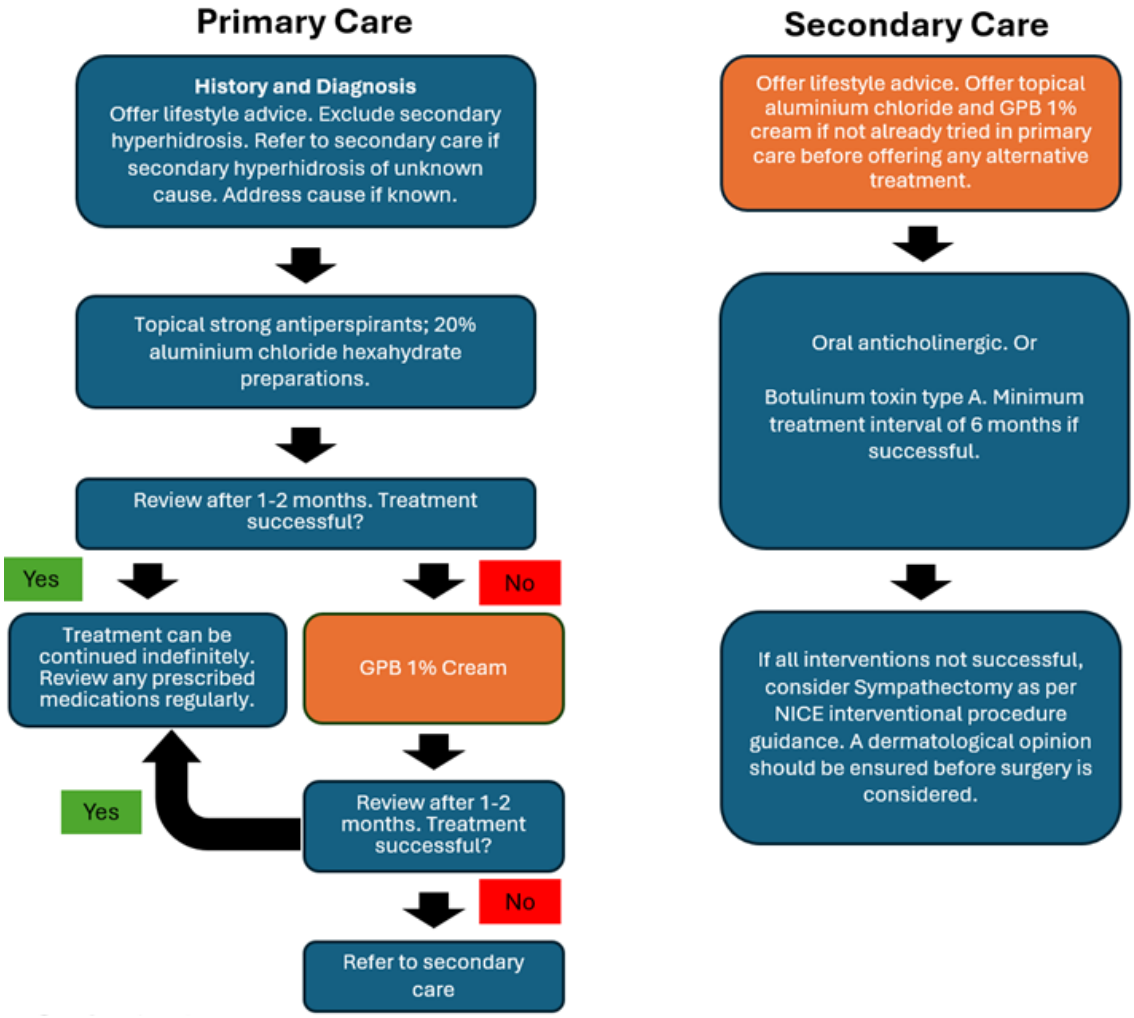
2.2.1.1 Positioning of GPB 1% cream in the treatment pathway

The company's proposed positioning of GPB 1% cream is outlined in Figure 2 below. The EAG notes that the company has positioned GPB 1% cream as a replacement for oral anticholinergics in primary care and that the figure suggests that the company proposes that GPB 1% cream will displace the use of oral anticholinergics to secondary care (Figure 2). In addition, the EAG notes that Figure 2 does not include topical glycopyrrolate as a treatment option in the box containing botulinum toxin A, suggesting that glycopyrronium bromide (glycopyrrolate) 2% w/w in cetomacrogol cream is no longer expected to be used in PAHH following the introduction of GPB 1% cream.

The EAG sought additional clarification from the company on the proposed positioning of GPB 1% cream and the company confirmed that GPB 1% cream is proposed as an alternative to oral anticholinergics in primary care and in secondary care where patients have not tried oral anticholinergics in primary care (company response to clarification question A1). The company

stated in their clarification response that they anticipated the main population to be in primary care and that GPB 1% cream is expected to displace the use of oral anticholinergics (e.g. oxybutynin) and botulinum toxin A in secondary care (company response to clarification question A29a). The EAG notes from Figure 2 that the company proposes that botulinum toxin A and oral anticholinergics will be secondary care treatment options following lifestyle advice, topical aluminium chloride and GPB 1% cream.

Figure 2. Proposed care pathway for PAHH with GPB 1% cream (reproduced from Figure 2 of the CS)



Abbreviations: GPB, glycopyrronium bromide; NICE, National Institute for Health and Care Excellence; PAHH, Primary Axillary Hyperhidrosis.

2.3 Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by NICE,[8] together with the rationale for any deviation from it, in Section 1 of the CS. This is summarised in Table 28 below and more detailed comments from the EAG are provided in the subsections that follow. The EAG is concerned that the population in the key trial providing clinical evidence on GPB 1% cream (Hyp-18/2016 Phase 3a and

3b trial) does not align with the company's proposed position for GPB 1% cream in the UK treatment pathway. In addition, the EAG is concerned about the reliability of the evidence from the company's ITCs.

Table 28. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	Adults with severe primary axillary hyperhidrosis.	Adults with severe primary axillary hyperhidrosis.	N/A	The EAG considers the population covered in the company's decision problem to align with the NICE final scope and the anticipated marketing authorisation for GPB 1% cream in PAHH but is concerned that the prior hyperhidrosis treatments of the patients in the Hyp1-18/2016 Phase 3a and 3b trials do not align with the company's proposed positioning of GPB 1% cream in the treatment pathway. See Section 2.3.1 for further discussion.
Intervention	Glycopyrronium bromide 1% cream.	GPB 1% cream.	N/A	The intervention covered in the CS and the clinical trial data from Hyp1-18/2016 Phase 3a is consistent with the NICE final scope and the expected marketing authorisation for GPB 1% cream in people with PAHH. However, the EAG is concerned that the placebo patients from Hyp-18/2016 Phase 3a that enrolled in Hyp1-18/2016 Phase 3b may not have received the anticipated marketing authorisation recommended once-daily treatment with GPB 1% cream for the first 4 weeks in Phase 3b. Further details are provided in CS Section 1.1, company

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
				response to clarification question A8 and Section 2.3.2 below.
Comparator(s)	• Oral antimuscarinics such as propantheline bromide, off-label oxybutynin or off-label oral glycopyrronium bromide. Botulinum-toxin A (Botox) injection.	• Oral antimuscarinics such as propantheline bromide, off-label oxybutynin or off-label oral glycopyrronium bromide. Botulinum-toxin A (Botox) injection.	N/A	The EAG notes the company's proposed positioning of GPB 1% cream is mainly for use in primary care and the EAG considers that oral anticholinergics are likely to represent the most appropriate comparator for GPB 1% cream in primary care. The EAG notes that the company has conducted indirect treatment comparisons for GPB 1% cream versus both oral antimuscarinics and botulinum toxin A. See Section 2.3.3 for further details.
Outcomes	The outcome measures to be considered include: • disease severity; • absolute change in sweat production; • response rates; • adverse effects of treatment; • health-related quality of life.	The outcome measures to be considered include: • disease severity; • absolute change in sweat production; • response rates; • adverse effects of treatment; • health-related quality of life.	N/A	All outcomes specified in the NICE final scope were captured in the Hyp1-18/2016 Phase 3a and 3b trials and reported in the CS. See Section 2.3.4 for further details.
Economic analysis	The reference case stipulates that: - the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year; and	-	-	Adheres to the NICE final scope. However, the EAG considers that even though the time horizon is lifetime, no difference in mortality is assumed and patients spend the majority of the model time horizon in the subsequent

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
	the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.			treatment health state, where only costs are incurred and not the benefits of treatment. Consequently, the EAG considers that a lifetime horizon may introduce unnecessary "noise" into the results and instead, the EAG prefers a shorter time horizon of two years. See Section 4.2.2.1 for further details.
Subgroups	None specified in NICE final scope.	-	N/A	-

Abbreviations: CS, company submission; EAG, External Assessment Group; GPB, glycopyrronium bromide; N/A, not applicable; NICE National Institute for Health and Care Excellence.

2.3.1 Population

The EAG notes that the clinical evidence for GPB 1% cream in the CS is derived from the Hyp-18/2016 Phase 3a and 3b trial, with Phase 3a comprising a randomised controlled trial of GPB 1% cream versus placebo and Phase 3b comprising a single-arm study of GPB 1% cream. The population specified in the NICE final scope was adults with severe PAHH and this aligns with the population in the Hyp-18/2016 Phase 3a and 3b trial. The Hyp-18/2016 Phase 3a and 3b trial required patients to be aged 18 to 65 years at the time of informed consent and to have a diagnosis of severe PAHH with a HDSS score of 3 or 4.

In the company's economic model, baseline characteristics are derived from the full analysis set (FAS) population of the Hyp1-18/2016 Phase 3b trial of GPB 1% cream (see Section 3.2 for further information on the trial). Table 29 presents the baseline characteristics included in the economic model. Baseline Hyperhidrosis Disease Severity Score (HDSS) informs the initial distribution of patients across the HDSS health states at the start of the model time horizon, and this is discussed further in Section 4.2.2.

Table 29. Patient baseline characteristics included in the model – Hyp1-18/2016 Phase 3b trial FAS population (adapted from Table 21 and Table 22 of the CS)

Parameter	Mean value
Baseline age (years)	35.6
Proportion female	52.9%
Baseline HDSS distribution	
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]

Abbreviations: FAS, Full Analysis Set; HDSS, Hyperhidrosis Disease Severity Score, SD, standard deviation.

The EAG's clinical expert reported that the population in the Hyp-18/2016 Phase 3a and 3b trials was broadly representative of the expected population in UK clinical practice but noted a few potential differences (please see Appendix 7.1 for the trial's baseline characteristics). These differences included a slightly higher proportion of females expected in their clinical practice, and a greater proportion of black, Asian and other patients compared to in the Hyp-18/2016 Phase 3a and 3b trials, but the expert also highlighted that there is likely to be some variation across the UK.

The company's proposed positioning of GPB 1% cream is for use after lifestyle advice and topical aluminium chloride preparations, but the EAG notes that inclusion criteria for the Hyp-18/2016 Phase 3a and 3b trials do not appear to specify any requirements regarding prior treatment with topical aluminium chloride preparations. However, the EAG notes that concomitant treatment with antiperspirants with <20% aluminium-containing compounds cholinomimetic and anticholinergic treatment, muscle relaxants and drugs that may have muscle-relaxant action, and oral herbal medicine and topical treatments for hyperhidrosis were prohibited from 1 week before the gravimetric measurement screening (Visit 2a) until Week 72. The company response to clarification question A30 detailed that 7 patients in Hyp1-18/2016 Phase 3a were recorded as having received prior hyperhidrosis treatment and that these comprised of mainly deodorants and aluminium-containing deodorants. The EAG notes that 171 patients were enrolled in the Full Analysis Set for Hyp-18/2016 Phase 3a (FASa) and these data suggest that only 4.1% of patients had received prior hyperhidrosis treatment. For the newly recruited patients in Hyp1-18/2016 Phase 3b (FASnewb), 52 of the 357 patients (14.6%) had at least 1 previous treatment for hyperhidrosis and [redacted]

The company reported that sensitivity analyses were conducted for patients in the FASnewb population, excluding patients who used deodorants containing aluminium chloride and excluding patients who used deodorants that possibly contained aluminium. However, the EAG notes that while the use of aluminium free deodorants was permitted from week 4 onwards, the use of aluminium containing deodorants was prohibited from either screening Visit1a/b onward (antiperspirants with ≥20% aluminium-containing compounds) or from 1 week before the gravimetric measurement screening (Visit 2a) until Week 72 (antiperspirants with <20% aluminium-containing compounds). The EAG considers it to be unclear whether the patients who used the aluminium-containing deodorants in FASnewb were the same patients who had received prior treatment with aluminium-containing deodorants. The EAG is therefore unsure of the relevance of the sensitivity analyses referred to by the company with regards to the impact of prior hyperhidrosis treatment with aluminium-containing deodorants on GPB 1% cream.

In summary, the EAG is concerned that the population in the Hyp-18/2016 Phase 3a and 3b trials does not align with the proposed population in UK clinical practice in terms of prior treatments based on the company's proposed positioning for GPB 1% cream, and the EAG is therefore concerned about the generalisability of the results from the Hyp-18/2016 Phase 3a and 3b trial to the company's proposed positioning of GPB 1% cream in UK clinical practice (**Key issue 1**, Section 1).

The EAG is particularly concerned that patients who have failed on first-line treatments may potentially be more challenging to treat and so may be less likely to respond to subsequent treatments.

2.3.2 Intervention

The intervention specified in the NICE final scope was GPB 1% cream and this reflects the intervention in both the CS and the Hyp-18/2016 Phase 3a and 3b trial.

Glycopyrronium (GP) inhibits acetylcholine-driven sympathetic actions on various exocrine glands such as sweat glands, resulting in a reduction in sweat production.

The MHRA granted UK marketing authorisation for GPB 1% cream for the topical treatment of severe primary axillary hyperhidrosis in adults in June 2025.[1] The company reported that GPB 1% cream is for topical use in the underarm area only and not for use in other body areas. In addition, the company reported that the safety and efficacy of GPB 1% cream in children and adolescents aged 12–18 years has been shown in a clinical trial,[9] and is currently under review by authorities, although the EAG notes that only data in the adult population were provided in the CS.

The recommended dose for GPB 1% cream is two pump actuations per axilla, which is equivalent to 0.54g (1.08g in total for both axillae).[10] The treatment regimen for GPB 1% cream is once daily application to each axilla for four weeks, and then a minimum application of twice per week from week five onwards. The Summary of Product Characteristics (SmPC) for GPB 1% cream recommends continuous usage to maintain the treatment effect.[10] The dose and treatment regimen for GPB 1% cream included in the economic model is aligned with the SmPC.

The EAG notes that patients in the placebo arm of Hyp-18/2016 Phase 3a who entered Phase 3b received GPB 1% cream as needed from the start of Phase 3b (at least twice per week but at most once daily) and [redacted]. The EAG is unsure what impact this potential discrepancy in treatment may have had (if any) on the overall results of Phase 3b, but notes that the company considers the full effect of the cream would be visible after 4 weeks (week 8 for placebo patients from 3a entering 3b, [redacted][company response to clarification question A8]). In addition, the company reported that the primary efficacy outcome in Phase 3b was only evaluated in the full analysis set (FAS) newly recruited patients in the 3b part (newb) with the dosing scheme 4 weeks daily and thereafter as needed (at least twice per

week but at most once daily). Secondary efficacy data in Hyp1-18/2016 Phase 3b were assessed from week 12 for all patients (FASb). However, the EAG is concerned with the reliability of the FASb data, and notes that week 4 data for HDSS from the FASnewb population appear to have been used in the company's economic model with FASb data used for the later timepoints.

The EAG notes that based on the company's proposed positioning of GPB 1% cream in the current treatment pathway it could be used in both primary and secondary care settings (Figure 2). However, the economic model does not make a distinction between healthcare settings, instead implementing proportions of the type of care setting used for administration and monitoring of patients on GPB 1% cream and the comparators (**Key issue 2**, Section 1). This is discussed further in Section 4.2.2.1.

2.3.3 Comparators

The comparators specified in the NICE final scope were:

- oral antimuscarinics such as propantheline bromide, off-label oxybutynin and off-label oral glycopyrronium bromide; and
- botulinum toxin A (Botox®) injection.

The EAG notes that the company's proposed positioning of GPB 1% cream is as an alternative to oral anticholinergics in primary care, and in secondary care where patients have not tried oral anticholinergics in primary care (company response to clarification question A1). The EAG also notes that oral antimuscarinics, as detailed in the NICE final scope, comprise a subset of oral anticholinergics.

The EAG considers that oral anticholinergics are likely to represent the most appropriate comparator for GPB 1% cream in primary care based on the company's proposed positioning and clinical expert advice that botulinum toxin A is not typically available in primary care. The EAG also notes, based on advice from its clinical experts, that propantheline bromide is likely to be the most frequently used oral anticholinergic in primary care as it is currently the only oral anticholinergic with UK marketing authorisation for use in hyperhidrosis.

The EAG notes that the anticipated marketing authorisation for GPB 1% cream is not expected to restrict treatment based on prior treatments, although the company is positioning it after lifestyle advice and topical 20% aluminium chloride hexahydrate preparations, such as roll-on antiperspirants

and sprays. However, as detailed in Section 2.3.1, the EAG is concerned that the population in the Hyp-18/2016 Phase 3a and 3b trial does not align with the company's proposed positioning of GPB 1% cream in UK clinical practice with regards to prior treatments (**Key issue 1**, Section 1). This is because less than 15% of patients in FASa (Hyp-18/2016 Phase 3a) and FASnewb (Hyp-18/2016 3b) had a documented history of prior treatments for hyperhidrosis.

The EAG notes that potential comparators for GPB 1% cream in secondary care are both oral anticholinergics and botulinum toxin A and given the lack of head-to-head trial data the company has conducted indirect treatment comparisons to provide estimates of effectiveness for GPB 1% cream versus antimuscarinics and GPB 1% cream versus botulinum toxin A. The ITCs are used in the economic model and are discussed further in Section 4.2.3.

In the economic model, the company assumed a weighted basket for oral antimuscarinics, with the proportions and treatment regimens for each presented in Table 30. The company states that proportions on each oral antimuscarinic are derived from a study by Wade *et al.,* 2017.[11]

For botulinum toxin A, the company assumed that the dose per axilla would be 50U (100U in total), based on the SmPC, clinical expert advice and the clinical trial data informing the indirect comparison, described in Section 3.4. In scenario analyses, the company explored doses of 75U per axilla (150U in total) and an average of 50U and 75U per axilla.

Table 30. Proportions and treatment regimens of oral antimuscarinics included in the company's economic model (reproduced from Table 25 of the CS)

Drug	Proportion	Treatment regimen
Propantheline bromide	35.4%	15 mg 3 times a day and 30mg before bed (75mg/day)
Oxybutynin	46.2%	2.5 mg 3 times a day (7.5mg/day)
Oral GPB	18.5%	2mg once a day

Abbreviations: GPB, glycopyrronium bromide; mg, milligram.

2.3.4 Outcomes

The outcomes specified in the NICE final scope were all reported in the Hyp-18/2016 Phase 3a and 3b trial with results reported in the CS and/or CSR:

- disease severity;
- absolute change in sweat production;
- response rates;

- adverse effects (AEs) of treatment; and
- health-related quality of life.

Absolute change in sweat production assessed by gravimetry from Baseline to Day 29 in the GPB 1% cream group compared with the placebo group was the primary efficacy endpoint in Hyp-18/2016 Phase 3a and absolute change in total sweat production assessed by gravimetry from Baseline to Week 12 in newly recruited patients was the primary efficacy endpoint in Hyp-18/2016 Phase 3b.

The percentage of responders assessed by the hyperhidrosis disease severity scale (HDSS; ≥2-point improvement from baseline) was captured from Baseline to Day 29 in Hyp-18/2016 Phase 3a, and from Baseline to Week 12 and Baseline to Week 28 in Hyp-18/2016 Phase 3b as part of the secondary efficacy endpoints.

As discussed in Section 2.1, disease severity in PAHH is classified using the HDSS score. The EAG notes that data on patients with improvement in HDSS of ≥2, ≥1 and 1 or 2 at weeks 4, 8, 12, 28, 52, and 72 with GPB 1% cream in Hyp-18/2016 Phase 3b were used in the company's economic model. In addition, the EAG notes that median change from baseline in HDSS was reported in Hyp-18/2016 Phase 3a and 3b, and the EAG requested for outcome data to be provided as mean values during the clarification stage (clarification question A10). The EAG discusses these data further in Section 3.3.2.

In terms of quality of life, absolute change in the hyperhidrosis quality of life index (HidroQoL) from Baseline to Day 29 in the GPB 1% cream group compared with the placebo group in Hyp-18/2016 Phase 3a, and from Baseline to Week 12 in Hyp-18/2016 Phase 3b were secondary outcomes. The Dermatology Life Quality Index (DLQI), which is a more general measure of quality of life, was also captured in both Hyp-18/2016 Phase 3a and 3b.

Safety outcomes in studies Hyp-18/2016 Phase 3a and 3b included the frequency, severity and relation of AEs, serious AEs (SAEs), treatment-emergent AEs (TEAEs), suspected unexpected serious adverse reactions (SUSARs), and discontinuations due to AEs. The EAG notes that the economic model included TEAEs for GPB 1% cream occurring in ≥2% of patients in the Phase 3b part of the Hyp1-18/2016 study.

In summary, the EAG considers that data for the outcomes from the NICE final scope are available from Hyp-18/2016 Phase 3a and 3b

3 Clinical effectiveness

This section presents a summary and critique of the clinical-effectiveness evidence included in the company's submission (CS). Section 3.1 focuses on the company's review of clinical and safety evidence. Sections 3.2 to 3.3 provide a critique of the included studies and clinical-effectiveness analyses. Section 3.4 critiques the indirect treatment comparisons presented by the company and Section 3.5 presents the conclusions.

3.1 Critique of the methods review

The company conducted a clinical systematic literature review (SLR) to identify all published evidence (including randomised and non-randomised studies, and comparative and single-arm studies) relating to the clinical efficacy, safety and tolerability of 1% glycopyrronium bromide (GPB) cream and established treatments for severe axillary hyperhidrosis, outlined in Appendix B of the company submission.

The External Assessment Group (EAG) summarises the SLR methods in Table 83 (Appendix 7.2). A wide range of evidence sources were searched, including the key databases as well as relevant conference proceedings, health technology appraisal (HTA) organisations and clinical trial registers. Search strategies appear to be overly complex, and the thoroughness of terms used appears to differ between databases. The EAG considers these important to address if the review was updated or if non-randomised evidence for comparator treatments became important for the submission, but on review of some other published SLRs the EAG is reassured that at this point in time it is unlikely that any additional randomised controlled trials (RCTs) likely to be candidates for inclusion in the indirect treatment comparisons (ITCs) have been missed. Inclusion criteria appear appropriate and are slightly broader than that outlined in the National Institute for Health and Care Excellence (NICE) final scope for population,[12] allowing evidence from indirect populations to be considered in the absence of evidence directly matching the population of interest in this appraisal. Processes for screening, data extraction and quality assessment appear to be appropriate, although details of quality assessment for non-randomised studies included in the SLR are not provided.

Overall, the EAG considers that some amendments to the search strategies would be useful in terms of improving robustness and reducing the risk of studies being missed, and that more details regarding quality assessment of non-randomised studies could be provided. However, it does not consider these to be major issues based on a review of other SLRs in the area and considering non-

randomised evidence for comparator treatments has not been utilised in the clinical section of this appraisal.

3.2 Critique of trials of the technology of interest

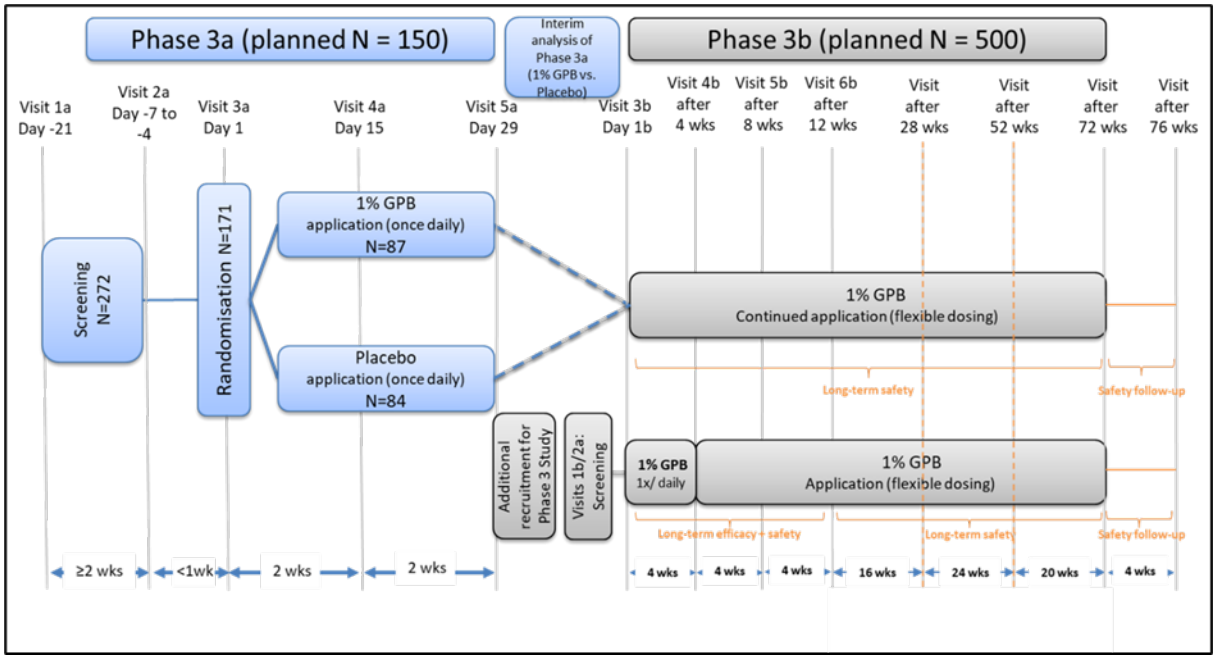
The company reported that their SLR identified two publications describing the Hyp-18/2016 Phase 3a and 3b trial, which provide the key clinical efficacy evidence on GPB 1% cream for the treatment of severe PAHH in adults aged 18 years or older in the CS and economic model.[13, 14] The company also provided details of a related Phase 1b study (NCT03037788)[15, 16] in the CS. The EAG notes that the Phase 1b study was a small (N=30) single-centre (Germany) study comparing GPB 0.5%, 1% and 2% creams with placebo, and comprising of a two-week treatment period with follow-up to day 21. The EAG also notes the Hyp-18/2016 Phase 3a and 3b trial comprised a larger sample size, with all patients on the dose of GPB cream in the UK marketing authorisation and the Phase 3b part of the study included up to 72 weeks of treatment. The Phase 1b study is not discussed further in this report as it was not used to inform the economic model and no results were reported in the CS. The EAG's critique of the design and conduct of the Hyp-18/2016 Phase 3a and 3b trial is summarised below and in Table 31.

The Hyp-18/2016 Phase 3a trial was a randomised, double-blind study that was designed to compared the efficacy and safety of topical 4-week treatment with GPB 1% cream versus placebo cream (vehicle cream without active ingredient).[13] The Hyp1-18/2016 Phase 3a trial was followed by an open-label Phase 3b extension[14] to assess the long-term efficacy and safety of GPB 1% cream in patients with severe PAHH with treatment allowed up to week 72 and follow-up until week 76. The Phase 3a part was conducted at 21 centres across Germany, Hungary, United Kingdom (UK), Denmark, and Sweden and the Phase 3b part also included centres in Poland and comprised a total of 37 centres.

Hyp-18/2016 Phase 3a, a total of 171 patients were randomised in a 1:1 ratio to once-daily treatment with GPB 1% cream (87 patients) or placebo cream (84 patients) for 4 weeks (Figure 3). Safety and efficacy were assessed following 14 and 28 days of treatment (at Day 15 and Day 29/end of treatment [EOT]a) and at the EOTa visit, all patients were offered to continue open-label treatment with GPB 1% cream (Phase 3b part), irrespective of the treatment applied during the Phase 3a part. There were 166 patients who completed the Phase 3a part, and 161 patients continued in the 3b part of the study. For patients progressing from Hyp1-18/2016 Phase 3a to Phase 3b, the Day 29/EOTa corresponded to Week 4 of the Phase 3b part (Figure 3).

In addition to patients entering Phase 3b from Phase 3a, a further 357 patients were included in Phase 3b, and these patients are referred to as 'newly recruited patients'. Treatment in Phase 3b was for up to 72 weeks and all 518 patients were treated with GPB 1% cream. The newly recruited patients applied GPB 1% cream once daily for the first 4 weeks (consistent with treatment during Phase 3a). After completion of Week 4 in Phase 3b, all patients (including those who rolled over from the Phase 3a part of the study) could apply GPB 1% cream as needed (at least twice per week but at most once daily) up to Week 72/EOTb, followed by a 4-week safety follow-up (Week 76).

Figure 3. Flow chart of the study design for Hyp1-18/2016 (reproduced from Figure 3 of the CS)



Source: Hyp-18/2016 Phase3a/b CSR[29]

Abbreviations: GPB, glycopyrronium bromide; wks, weeks.

[redacted]

The EAG also considers the outcome assessment time periods to be potentially confounded by the difference in treatment for the placebo roll-over patients from Phase 3a to 3b. This is because Phase 3b Week 8 for the placebo Phase 3a patients who entered Phase 3b is actually only Week 4 of treatment with GPB 1% cream. In contrast, for the GPB 1 % cream patients from Phase 3a and the newly recruited patients, Week 8 in Phase 3b reflects 8 weeks of treatment with GPB 1% cream and these 8-weeks of treatment are consistent with the marketing authorisation recommended treatment regimen. The EAG is unsure what impact this potential discrepancy in treatment may have had (if any) on the overall results of Phase 3b, but notes that the company considers the full effect of GPB 1% cream would be visible after 4 weeks (week 8 for placebo patients from 3a entering 3b, [redacted] [company response to clarification question A8]). The EAG also notes that the company reports only secondary efficacy outcomes would be affected by this potential discrepancy and that these are assessed from Week 12 onwards. However, the EAG notes that data for change in HDSS from baseline for the full analysis set in Phase 3b (FASb) are used in the company's economic model from Week 8 and that only FAS newly recruited patients in Phase 3b (newb) were used to inform the data at Week 4.

The EAG notes that during Phase 3a patients were not allowed to use any concomitant deodorants or antiperspirants but during Phase 3b from week 4 onwards the use of aluminium-free deodorants was permitted. The EAG is unsure how reflective this is of how GPB 1% cream would be used in UK clinical practice. In addition, as discussed in Section 2.3.1, the EAG is concerned that the prior treatments of patients in Phase 3a and newly recruited patients in Phase 3b do not appear to reflect the population in the company's proposed positioning of GPB 1% cream in UK clinical practice. The Hyp-18/2016 Phase 3a and Phase 3b trial parts both comprised of fewer than 15% of patients with prior hyperhidrosis treatments, whereas the company's primary proposed positioning of GPB 1% cream is following lifestyle advice and topical 20% aluminium chloride hexahydrate preparations, such as roll-on antiperspirants and sprays.

In summary, the EAG is concerned that the prior treatments of patients in Phase 3a and Phase 3b do not reflect the company's proposed positioning of GPB 1% cream in UK clinical practice and the data in Phase 3b may be confounded by differences in the treatment regimen for patients enrolled from the placebo arm of Phase 3a. In addition, the EAG is concerned by the open-label nature of Phase 3b and potential reporting bias, particularly for the subjective outcomes such as HDSS change from baseline, which is the key outcome informing the efficacy of GPB 1% cream in the economic model.

Table 31. EAG's summary of the design, conduct and analysis of Hyp1-18/2016 Phase 3a and Phase 3b trial

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	2.4.3 and 2.5	**Appropriate for Phase 3a but no randomisation in Phase 3b** Patients were randomly assigned dispensers containing GPB 1% cream or placebo cream using a computer-generated randomisation list with a 1:1 allocation in Phase 3a. The randomisation was performed centrally with no stratification and permutated blocks with a block size of 4 were used. Phase 3b was a single arm open-label study with no randomisation.
Concealment of treatment allocation	2.4.3 and 2.5	**Appropriate for Phase 3a but Phase 3b was open-label** In the CS it is reported that eligible patients were assigned numbers in ascending order beginning with the lowest available number and the EAG notes from the CSR that randomisation information was kept confidential by the responsible sponsor personnel and not disclosed to the investigator or other study centre personnel until after database lock for the interim analysis of Phase 3a. Treatment allocation was not concealed for Phase 3b and all patients received GPB 1% cream.
Eligibility criteria	2.3.2.2	**Likely to be appropriate for Phase 3a and Phase 3b** The inclusion criteria included: • diagnosis of severe primary axillary hyperhidrosis with a HDSS score of 3 or 4; • at least 50 mg of sweat production in each axilla measured gravimetrically at room temperature and at a humidity consistent with the normal climate in that area over a period of 5 minutes (patients should have acclimatised to that room for at least 30 minutes); • men and women aged 18 to 65 years at the time of informed consent with a body mass index (BMI) of 18-32 kg/m2. The exclusion criteria included: • secondary hyperhidrosis, e.g. hyperhidrosis secondary to other underlying diseases such as hyperthyroidism and lymphoma; • previous surgical treatment of hyperhidrosis including sympathectomy, surgical debulking of the sweat glands, subcutaneous tissue curettage and ultrasonic surgery; • botulinum toxin treatment for the treatment of axillary hyperhidrosis in the previous 4 months. The EAG's clinical expert reported that few PAHH patients in UK clinical practice would have a BMI over 32 but it is unclear why study enrolment was restricted by BMI. The EAG also notes that there is no restriction in the MHRA SPC for GPB 1% cream use in PAHH based on BMI. In general, the EAG considers the population enrolled in the Phase 3a and 3b parts to align with the population specified in the NICE final scope (adults with severe PAHH).

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Blinding	2.4.3	**Appropriate for Phase 3a but Phase 3b was open-label with no blinding reported so high risk of bias, particularly for subjective outcome measures such as HDSS change from baseline** Study participants, investigators, the sponsor, and all other persons involved in the conduct of the study were blinded to the treatment during the randomised double-blind Phase 3a part of the study. The GPB 1% cream and placebo cream had identical appearance, texture, and smell, and were labelled and packaged identically. Phase 3b was open label and no blinding of outcome assessment was reported in the CS.
Baseline characteristics	2.3.2.3 and 2.3.2.4	**Some minor imbalances between arms and some discrepancies compared to the UK population, particularly regarding prior hyperhidrosis treatments** According to the EAG's clinical expert, the populations in Hyp1-18/2016 Phase 3a and Phase 3b were broadly representative of the expected population in UK clinical practice but it was noted that there are a few potential differences although there is likely to be variation across the UK. These differences included a slightly higher proportion of females expected in their clinical practice and a greater proportion of black, Asian and other patients compared to in Hyp-18/2016 Phase 3a and Phase 3b. [redacted]whereas the company's primary proposed positioning of GPB 1% cream is following lifestyle advice and topical 20% aluminium chloride hexahydrate preparations, such as roll-on antiperspirants and sprays.
Dropouts	2.3.2.2, 2.3.2.3, 2.5, and 3.3.3.1	**No major concerns for Phase 3a but concerns that study discontinuation in Phase 3b was reasonably high (28%)** In Phase 3a only 3 (3.4%) patients in the GPB 1% treatment group withdrew and 2 (2.4%) patients in the placebo group. However, 150 (29.0%) of patients in Phase 3b discontinued the study before completing the end-of-study visit. The main reasons for discontinuation in Phase 3b were withdrawal of consent (55 patients; 10.6%), lost to follow-up (43 patients; 8.3%), other reasons (36 patients; 6.9%), and one reported death (0.2%).
Statistical analysis		
Sample size and power	2.4.3	**Likely to be appropriate** For Phase 3a, a sample of N = 63 per group was deemed to be sufficient to detect an effect size of 0.5 between the placebo and the GPB 1% cream groups in sweat production with a power = 0.9 and α = 0.05 using a 2-sided t-test. Considering dropouts (about 15%), a sample size of N = 75 per group was calculated for Phase 3a and this was exceeded with 87 patients randomised to GPB 1% cream and 84 patients randomised to placebo. For Phase 3b, a sample size of 500 patients was considered sufficient to assess the safety of GPB 1% cream and following recruitment of newly treated patients there were a total of 518 patients in the FASb.

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Handling of missing data	2.4.3 and 2.5	**Appears to be reasonable for the key outcome of relevance (HDSS score)** The full analysis set for Phase 3a (FASa) was used for the evaluation of all efficacy endpoints from Phase 3a and this comprised of all patients randomised and treated at least once with an IMP in the Phase 3a part with patients analysed as per the intention-to-treat (ITT) principle (i.e. in the treatment group as randomised). For Phase 3a, patients with missing values at Baseline or Day 29 were considered non-responders for the HDSS secondary endpoint. *Post hoc* analysis was conducted for this endpoint, excluding missing values from the analysis. The full analysis set for Phase 3b (FASb) was used in analyses of all secondary endpoints in Phase 3b and comprised of all patients who received at least 1 dose of IMP in Phase 3b. The FASnewb was a subset of the FASb and was used for the evaluation of the primary and all secondary endpoints regarding only newly recruited patients. For Phase 3b, patients with missing values for HDSS were considered as non-responders in keeping with the analysis of Phase 3a. [redacted]
Outcome assessment	2.2 and CSR	**Appropriate** The EAG considers the outcomes assessed to be appropriate and cover those requested in the NICE final scope. The primary efficacy outcome in Phase 3a was absolute change in sweat production assessed by gravimetry from Baseline to Day 29 in the GPB 1% cream group compared with the placebo group and in Phase 3b it was absolute change in total sweat production assessed by gravimetry from Baseline to Week 12 assessed in only the newly recruited patients to Phase 3b. HDSS change from baseline and percentage of responders based on HDSS score (≥2-point improvement from baseline) were secondary outcomes, alongside other measures of HRQoL and adverse events. All relevant outcomes collected in Phase 3a and Phase 3b appear to have been reported either in the CS or the CSR. The EAG notes that median values were reported for some outcomes in the CS, but mean values have also been extracted by the EAG from the company response to clarification questions and the CSR where available.
Role in this evaluation	2.9 and 3.3	**Appears reasonable although EAG has concerns with the generalisability of the trial data as discussed in Section 2.3** Hyp-18/2016 Phase 3a is used in indirect treatment comparisons to provide clinical evidence for GPB 1% cream versus antimuscarinic and versus botulinum toxin A. Hyp-18/2016 Phase 3b is used to provide clinical effectiveness evidence for GPB 1% cream in the economic model (HDSS change from baseline and adverse effects).

Abbreviations: EAG, External Assessment Group; FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, hyperhidrosis disease severity scale; IMP, investigational medicinal product.

3.3 Critique of the clinical effectiveness analysis and interpretation

The EAG presents results for the key outcomes of relevance to the NICE final scope from the Hyp-18/2016 Phase 3a and Phase 3b trial in the sections that follow. Of the efficacy outcomes, only HDSS response was used in the company's economic model. Absolute change in sweat production was the primary efficacy outcome in Phase 3a and Phase 3b, and the results are discussed in Section 3.3.1, and quality of life measurements were captured as secondary outcomes, with results discussed in Section 3.3.3. It should be noted that only results for the full analysis sets are discussed and presented in this report, except for the HDSS responder analysis where per protocol results are also summarised for Phase 3b as they were used by the company in a scenario analysis.

Hyp-18/2016 Phase 3a included a total of 171 randomised patients (GPB 1% cream N=87 and placebo cream n=84). Phase 3b included 518 patients, all treated with GPB 1% cream, and 357 of these were newly recruited patients. The maximum follow-up for efficacy outcomes was 29 days from baseline in Hyp1-18/2016 Phase 3a and 72 weeks in Hyp1-18/2016 Phase 3b.

3.3.1 Gravimetrically assessed sweat production

Gravimetrically assessed sweat production measurements were conducted at room temperature and at a humidity consistent with the normal local climate for each study centre. After an acclimatisation period of at least 30 minutes, axillary hair was trimmed, and the axillae were dried with a paper towel. Standardised filter paper was then placed on both axillae for 5 min, with the filter paper weighed before and after the gravimetric measurements in a central laboratory.

The primary endpoints (absolute change in sweat production) for both Phase 3a and Phase 3b were met. Absolute reduction in sweat production from baseline to day 29 for Phase 3a FASa in logarithmic values was [redacted] in the GPB 1% cream group compared to the placebo group ([redacted] [Table 32]). In addition, the absolute reduction in sweat production from baseline to Week 12 for Phase 3b FASnewb in logarithmic values was [redacted] [Table 32]).

Table 32. Absolute change in sweat production from baseline for Phase 3a (FASa), and Phase 3b newly recruited patients (FASnewb) (adapted from Table 15 and Table 17 of the CSR)[17]

Sweat production	Phase 3a FASa (N=171)		Phase 3b FASnewb (N=357)
	GPB 1% cream (N=87)	Placebo cream (N=84)	GPB 1% cream (N=357)
Absolute values (mg), mean (SD)			
Baseline	[redacted]	[redacted]	[redacted]
Change to Day 29	[redacted]	[redacted]	[redacted]
Change to Week 12	[redacted]	[redacted]	[redacted]
Logarithmic values, mean (SD)			
Baseline	[redacted]	[redacted]	[redacted]
Change to Day 29	[redacted]	[redacted]	[redacted]
Change to Week 12	[redacted]	[redacted]	[redacted]
Mixed effects model for change from Baseline			
Change to Day 29 LSmeans (95% CI)	[redacted]	[redacted]	[redacted]
Change to Week 12 Estimate (97.06% CI)	[redacted]	[redacted]	[redacted]
Difference to placebo			
LSmeans (95% CI)	[redacted]		[redacted]

[redacted]

3.3.2 Response

The proportion of responders to treatment was determined based on gravimetrically measured sweat production, as well as on the hyperhidrosis disease severity scale (HDSS) and hyperhidrosis quality of life (HidroQoL) questionnaires in both Phase 3a and Phase 3b. The key outcome of relevance is HDSS given its role in the economic model but the results for percentage change in sweat and HidroQoL are also discussed briefly below. The EAG notes that the HDSS is a disease-specific tool that provides a qualitative measure of the severity of hyperhidrosis based on how it affects daily activities using a 4-point scale ranging from 1 to 4. Response based on HDSS was classified as a ≥2-point improvement in the HDSS assessment compared to baseline values in Phase 3a and Phase 3b.

The company reported that HidroQoL is a validated patient-reported outcome measure (PROM) used to capture the Quality of life (QoL) of patients with hyperhidrosis. It comprises of questions on daily life activity and psychosocial life with questions rated on a 3-point scale and a summary score for each domain and overall score calculated. In 2020, the HidroQoL was revalidated specifically for PAHH and the minimally clinically important difference (MCID) for treatment response was defined as an improvement of ≥ 4 points.[13] However, the EAG notes that the revalidation study was funded by a grant from Dr. August Wolff GmbH & Co. KG Arzneimittel, the sponsor of the Hyp1-18/2016 Phase 3a and Phase 3b trial.[18]

At day 29, [redacted] with GPB 1% cream than with placebo in Phase 3a ([redacted] [Table 33]). The company also reported that [redacted] patients in Phase 3a achieved a 50% reduction in sweating with the GPB 1% cream ([redacted]%) compared to with placebo ([redacted]%). For Phase 3b FASnewb patients, [redacted]% achieved a ≥ 50% reduction in sweat production at [redacted] the proportion in Phase 3a FASa ([redacted]%). The EAG notes that this outcome was not pre-specified or reported for the FASb population.

The HidroQoL responder analysis in Phase 3a was a *post hoc* analysis and [redacted] GPB 1% cream compared with placebo at Day 29 (difference in median [redacted], 95% confidence interval [95% CI]: [redacted] based on a minimal clinically important difference [MCID]of ≥ 4). Results for HidroQoL median change from baseline for the Phase3b FASb population are not directly comparable with the Phase 3a results due to differences in the methods, [redacted] in HidroQoL total score with GPB 1% cream at week 12 compared to baseline.

The HDSS response rate at day 29 in Phase 3a was numerically higher with GPB 1% cream (23.0%) compared with placebo (11.9%) but the difference between groups was not statistically significant (p = 0.054 [Table 33]).

[redacted]

[redacted]

Table 33. Summary of sweat reduction and HDSS response results from FASa (adapted from Table 20 and Table 32 of the CSR)[17]

Outcome measure	Number of patients (%)		Odds ratio (95% CI)[a] (n = 171)	p-value[b]
	1% GPB (N = 87)	Placebo (N = 84)		
Responder rate (sweat reduction of ≥50%, ≥75%, and ≥90%) assessed by gravimetric measurement at Day 29				
≥50% sweat reduction from baseline	[redacted]	[redacted]	[redacted]	[redacted]
≥75% sweat reduction from baseline	[redacted]	[redacted]	[redacted]	[redacted]
≥90% sweat reduction from baseline	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of responders as assessed by the HDSS (≥2-point improvement from Baseline) at Day 29				
HDSS response	20 (23.0)	10 (11.9)	0.44 (0.19 to 1.03)	0.0542

Patients with missing values were considered non-responders.

a Cochran-Mantel-Haenszel test.

b 2-sided, α=0.05.

Abbreviations: CI, confidence interval; FASa, full analysis set (Phase 3a); GPB, glycopyrronium bromide; HDSS, hyperhidrosis disease severity scale; N, number of patients; n, number of patients in the analysis.

[redacted]

[redacted]

The EAG notes that [redacted] patients were excluded from the PPSb population and the reasons for exclusion included early termination ([redacted]), time window violation ([redacted]), product use ([redacted]), and antiperspirant use ([redacted]). The EAG

[redacted]

[redacted]

Subgroup results based on prior treatment were not reported for the FASb population.

Table 34. Patients in FASb with improvement in HDSS in the Phase 3b FASb population (reproduced from Table 26 of the CS)

Week	>=2			>=1			1 or 2		
	N	N	%	N	N	%	N	N	%
4*	[redacted]								
8	[redacted]								
12	[redacted]								
28	[redacted]								
52	[redacted]								
72	[redacted]								

* Week 4 data are from FASnewb.

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Scale; N, number of patients.

Source: Table 41, Table 4.3.4_b, Table 4.4.3_b, and Table 6_b, CSR[17]

Table 35. Patients with improvement in HDSS in the Phase 3b PPSb population (reproduced from Table 27 of the CS)

Week	>=2		
	N	N	%
12	[redacted]		

28	[redacted]	[redacted]	[redacted]

Abbreviations: HDSS, Hyperhidrosis Disease Severity Scale; N, number of patients; PPS, per protocol set.
Source: Table 24, Table 25, CSR[17]

In response to clarification question A15, the company reported results from assessments of the correlations between total sweat production and HDSS scores for the FASnewb population (N=357) at baseline (r=[redacted]), week 4 (r=[redacted]), and week 12 (r=[redacted]), with [redacted]. In addition, the company reported that correlations between the absolute change in HDSS scores and the absolute change in sweat production from baseline to week 4 and week 12 were also low, with correlation coefficients of r=[redacted] and r=[redacted] at both time points (CS Figures 1 and 2).

The company considered that despite the lack of strong correlation between HDSS scores and gravimetric sweat reduction, HDSS remains a relevant and meaningful outcome for evaluating treatment effectiveness in PAHH. The EAG notes that HDSS is a patient-reported measure, whereas gravimetric sweat production is an objective assessment. The EAG's clinical expert reported that HDSS is used to help guide response to treatment in clinical practice, but the EAG considers it to be concerning that there is an apparent lack of correlation between sweat production and HDSS scores in Hyp-18/2016 Phase 3b newly recruited patients with GPB 1% cream (**Key issue 3**, Section 1).

3.3.3 Quality of life

Quality of life was captured in Hyp1-18/2016 Phase 3a and Phase 3b using the HDSS, HidroQoL and Dermatology Life Quality Index (DLQI) questionnaires; results are summarised below.

Median change in HDSS from baseline in Phase 3a for GPB 1% cream compared with placebo was statistically significant at both day 15 (p = 0.002) and day 29 (p = 0.014), suggesting improved QoL with GPB 1% cream. Median change in HDSS score from baseline with GPB 1% cream in Phase 3a was –1.0 at Day 15 and –0.0 at Day 29 (mean change at Day 29 was [redacted] with a standard deviation of [redacted]). Median change in HDSS score from baseline with GPB 1% cream in Phase 3b was [redacted].

In Phase 3a, [redacted] GPB 1% cream ([redacted]) compared with placebo [redacted]. Results from Phase 3b

FASb also showed a median improvement from baseline in HidroQoL total score and the individual domains at all timepoints from Week 4 to Week 72.[14]

The DLQI is a validated questionnaire used to measure the impact of skin disease on quality of life and comprises of 10 questions that are answered on a 4-point scale from 0 to 3 with higher scores representing a greater impact on QoL.[13, 19] The median improvement in DLQI was higher with GPB 1% cream (–5.0 points) compared to with placebo (–2.0 points) at Day 15 in Phase 3a, and the improvement with GPB 1% cream remained similar at Day 29 (–5.0 points). The difference in median between the GPB 1% cream and placebo was statistically significant at both Day 15 and Day 29 in Phase 3a (p = 0.002 and p = 0.003, respectively). Median reductions in DLQI score compared to baseline were also seen with GPB 1% cream at all time points in Phase 3b further suggesting an improvement in QoL with GPB 1% cream.[14]

The EAG notes that EQ-5D was not collected in the Hyp1-18/2016 trial. However, the EAG is aware that a validated mapping algorithm exists to map DLQI to EQ-5D.[20] The EAG requested the company explore mapping the pooled Hyp1-18/2016 3a and 3b DLQI data to EQ-5D at the clarification stage, but the company did not conduct this analysis (please see Section 4.2.6 for further detail]).

3.3.4 Safety

The company provides an overview of adverse events (AEs) within Phase 3a (GPB 1% cream and placebo arms) and 3b (all receiving GPB 1% cream) of the Hyp1-18/2016 trial in Section 2.6 of the company submission.[13, 14] The company also makes reference to a Phase 1b dose-finding study (Hyp-02/2015) that included GPB 1% cream and captured safety data as reported in the clinical study report (CSR) provided, but this only included [redacted] and as discussed in Section 3.2, it was not considered further by the EAG.[16] No indirect treatment comparisons (ITCs) have been performed for AEs, but in its economic modelling, AEs for comparator treatments have been informed by data from the studies used to perform ITCs against GPB 1% cream for the HDSS outcome, including Schollhammer *et al.* 2015 for oral antimuscarinics and Lowe *et al.* 2007 for botulinum toxin A,[21, 22] with GPB 1% cream AE data informed by data from Phase 3b of the Hyp1-18/2016 trial.[17]

The company presents a comparison of data for AEs considered for inclusion in the economic model between GPB 1% cream, oral antimuscarinics and botulinum toxin A in Table 32 of the company submission. The EAG successfully validated these data against the clinical study report (CSR) for GPB

1% cream (pages 1789 to 1798) and the publications for oral antimuscarinics,[17, 21] but considers the wrong data have been used for the 100U dose of botulinum toxin A; the 100U dose was focused on by the company to align with the rest of the model inputs for botulinum toxin A; however, the EAG considers the 150U dose data may have been erroneously included in Table 32 of the company submission, with corrections implemented in Table 36 below and corrected in the economic model by the EAG (see Sections 4.2.5 and 5.2.1).[22]

Only AEs for GPB 1% cream impacting at least 2% of patients up to week 72 of the Hyp1-18/2016 Phase 3b trial that were treatment-emergent and considered to be related to the treatment (termed adverse drug reactions; ADRs) were eventually included in the model. According to Table 36 below, this only included dry eye, dry mouth, application site erythema/flush and application site pruritus. On validating these data against the CSR,[17] the EAG notes that the application site pain ADR was also experienced by at least 2% of patients ([redacted]) but was not included in Table 36 below; given this is likely to be linked to the application site erythema pruritus ADRs that are captured in this table, the EAG does not consider this to be a major issue. The same 2% threshold was not said to be required for comparator treatments, but all of those included did happen to occur in at least 2% of patients in these studies. However, given the trial used to inform data for oral antimuscarinics was very small (n=30), most of the AEs included in the model for this treatment were only experienced by one patient using that treatment.[21]

The EAG notes that no requirement for severity of AEs has been required for inclusion in the economic model. In fact, AEs for [redacted], based on the following statements:

- The CSR of Phase 3b of the Hyp1-18/2016 trial states that [redacted].[17]
- Schollhammer *et al.* 2015 reported no serious adverse events with the oral antimuscarinic oxybutynin and no discontinuation of patients due to side effects with the treatment;[21]

- Lowe *et al.* 2007 reported no serious treatment-related AEs and no discontinuations due to treatment-related AEs for treatment with botulinum toxin A. Only two patients reported a severe case of dry mouth, with intensity not mentioned for other AEs.[22]

While the EAG accepts that Phase 3b of the Hyp1-18/2016 trial may be a better indicator of AEs that may occur with longer-term use of GPB 1% cream, it was concerned that it may not capture AEs occurring when the treatment is used daily for the first 4 weeks of treatment before switching to treatment at a reduced frequency, as outlined in the Summary of Product Characteristics (SmPC) and as used in Phase 3a of the Hyp1-18/2016 trial.[10, 13] However, on review of data in the CSR for Phase 3a (pages 1498 to 1499),[17] the EAG is satisfied that there are no additional ADRs occurring in at least 2% of patients that have not already been captured within Phase 3b of the Hyp1-18/2016 trial.

It should be noted that there are substantial limitations with comparing the data in Table 36 given the differences in time-point and also study design between the studies; data for GPB 1% cream come from a 72-week non-randomised trial whereas data for oral antimuscarinics and botulinum toxin A come from randomised controlled trials (RCTs), with one reporting at 6 weeks and the other at 52 weeks. Furthermore, there may be some differences in criteria required and definitions for AEs across the studies that may affect comparability to some extent; AEs included from Phase 3b of the GPB 1% cream trial are defined as treatment-emergent AEs assessed as possibly, probably, or certainly related to GPB 1% cream, or where the relationship was missing, occurring in at least 2% of patients, while Schollhammer *et al.* 2015 only mentions "side effects" with severity only described for dry mouth, and Lowe *et al.* 2007 does not report severity and defines AEs as treatment-related events occurring in ≥2% of patients.[17, 21, 22] Data in Table 36 below suggests that dry eye, dry mouth and application site reactions are the most common AEs likely to occur with GPB 1% cream (also outlined as the most common in the SmPC),[10] although a naïve comparison suggests that dry mouth occurred in a [redacted] of patients taking oral antimuscarinics. Injection site issues including bleeding and pain are issues associated with botulinum toxin A according to Lowe *et al.* 2007,[22] occurring in [redacted] of patients that was seen regarding application site AEs with GPB 1% cream in the Phase 3b trial for GPB 1% cream.

Clinical expert feedback to the EAG was that the proportion of patients experiencing some of the AEs outlined in Table 36 was higher than expected in UK clinical practice; non-axillary sweating/hyperhidrosis with botulinum toxin A was higher than expected and was said to be rare in clinical practice, as in their experience this either does not occur or patients actually report

improvement in other areas rather than worsening or onset, and blurred vision was also said to be rare, despite a value of 13% from the oral antimuscarinics trial.

Clinical expert feedback also outlined that most of the AEs listed in Table 36 would involve stopping treatment or reducing the dose rather than treating the AE, with the exception of dry mouth for oral antimuscarinics which would involve secondary care, and non-axillary sweating/hyperhidrosis, which the clinical expert had not seen in clinical practice and could not say how it would be treated. While some patients may seek treatment for some of the other AEs, it was noted that this would not often involve a general practitioner (GP) visit. In addition, with regards the modelling, the EAG consider that the most notable AEs mentioned in the National Institute for Health and Care Excellence (NICE) evidence summary for oxybutynin in hyperhidrosis and the SmPC for botulinum toxin A have been considered.[23, 24] Therefore, on review of the trial data and clinical expert feedback, while there may be some differences between treatments in terms of the profile of AEs that may be experienced, [redacted] that will likely not receive a specific treatment, with dose interruptions or reductions more likely, and comparisons between treatments is limited given the differences in study design, trial duration and sample size noted earlier.

Based on the feedback received from the clinical expert and the statement within the CSR for the Hyp1-18/2016 trial that [redacted], the EAG requested that the company explore a scenario with 0% non-axillary sweating for botulinum toxin A and another exploring the exclusion of AEs from the economic model completely (clarification questions [CQs] B7 and B8). While the latter was not provided by the company, the EAG has performed this scenario and prefers the exclusion of AEs completely from its base case (see Section 4.2.5.1).

Table 36. Adverse event comparison between studies (adapted from Table 32 of the CS)

	GPB 1% cream[17]		Oral antimuscarinics[21]		Botulinum toxin 100U[22] (original company data)		Botulinum toxin 100U[22] (EAG-corrected)	
N	518		30		104		104	
Weeks	72		6		52		52	
	N	%	n	%	n	%	n	%
Dry eye	[redacted]	[redacted]	0	0.0%	0	0.0%	0	0.0%
Dry mouth	[redacted]	[redacted]	13	43.3%	0	0.0%	0	0.0%
Application site erythema/flush	[redacted]	[redacted]	1	3.3%	0	0.0%	0	0.0%
Application site pruritus	[redacted]	[redacted]	0	0.0%	0	0.0%	0	0.0%
Headache	[redacted]	[redacted]	1	3.3%	0	0.0%	0	0.0%
Nausea	[redacted]	[redacted]	1	3.3%	0	0.0%	0	0.0%
Diarrhoea	[redacted]	[redacted]	1	3.3%	0	0.0%	0	0.0%
Gastro-oesophageal reflux/other GI disorders	[redacted]	[redacted]	1	3.3%	0	0.0%	0	0.0%
Asthenia/Somnolence	[redacted]	[redacted]	1	3.3%	0	0.0%	0	0.0%
Dizziness	[redacted]	[redacted]	1	3.3%	0	0.0%	0	0.0%
Blurred vision	[redacted]	[redacted]	4	13.3%	0	0.0%	0	0.0%
Urinary difficulty/other renal or urinary disorder	[redacted]	[redacted]	1	3.3%	0	0.0%	0	0.0%
Injection site pain	[redacted]	[redacted]	NA	NA	9	8.7%	12*	11.5%*
Injection site bleeding	[redacted]	[redacted]	NA	NA	6	5.8%	5*	4.8%*
Non-axillary sweating/hyperhidrosis	[redacted]	[redacted]	0	0.0%	6	5.8%	10*	9.6%*

Abbreviations: EAG, External Assessment Group; GI, gastrointestinal; GPB, glycopyrronium bromide; NA, not applicable.

*EAG-corrected values obtained from page 610 of the Lowe *et al.* 2007 paper by estimated numbers with event from percentages reported (12% injection site pain, 5% injection site bleeding and 10% non-axillary sweating) and sample size of 104 for the 100U treatment arm.

3.4 Critique of the indirect treatment comparison or multiple treatment comparison

The company conducted Bucher indirect treatment comparisons (ITCs) to enable comparisons between GPB 1% cream and antimuscarinics, and GPB 1% cream and botulinum toxin A. The trials included in the ITCs are detailed in Section 3.4.1 and the methods in Section 3.4.2 with the results summarised in Section 3.4.3.

3.4.1 Trials informing the indirect treatment comparison

3.4.1.1 GPB 1% cream

The Phase 3a clinical data from baseline to Day 29 are used to inform the relative efficacy of GPB 1% cream compared to placebo in the company's ITCs for the outcomes HDSS response defined by ≥2 point improvement in HDSS score and ≥1 point improvement in HDSS score. The EAG notes that the company has conducted ITCs in both the FASa and PPSa populations.

3.4.1.2 Antimuscarinics

The SLR did not identify any placebo-controlled data for antimuscarinics (including propantheline bromide, oxybutynin, or oral GPB) exclusively in patients with severe PAHH. The search was subsequently broadened to include all types of HH and this resulted in the identification of six studies of oxybutynin, but none for propantheline bromide or oral GPB. Four of the oxybutynin studies were subsequently excluded by the company due to a lack of suitable outcome data for HDSS response and a further study was excluded due to the wrong population (it comprised of patients with secondary hyperhidrosis). The remaining study, Schollhammer *et al.* 2015[21], was included in the ITCs to provide data on antimuscarinics.

Schollhammer *et al.* 2015 was a randomised placebo-controlled trial (N = 62) conducted in France and reported on improvement in HDSS scores after 6 weeks. Oxybutynin was commenced at a dose of 2.5mg with dose escalation to 5mg from Day 5 and 7.5mg from Day 8 onwards. The EAG notes that while 75% of patients in the oxybutynin group had axillary hyperhidrosis, only 17% of patients had a localised form of hyperhidrosis (e.g. facial, palmar, axillary). The EAG also notes that the GPB 1% cream trial is in patients with PAHH and considers it to be unclear whether inclusion was restricted to patients with focal disease but potentially there is a discrepancy in the patient populations between Hyp-18/2016 Phase3a and Schollhammer *et al.* 2015 due to the large proportion of patients with generalised hyperhidrosis in Schollhammer *et al.* 2015. In addition, the EAG notes that patients with a baseline HDSS of 2 and above were eligible for inclusion in Schollhammer *et al.* 2015, whereas Hyp-18/2016 Phase3a restricted inclusion to HDSS scores at baseline of 3 or 4. In total 8.3% of the population in Schollhammer *et al.* 2015 had a baseline HDSS of 2, 58.3% had a HDSS score of 3 and 33.3% had a HDSS score of 4. [redacted] The Hyp-18/2016

Phase3a population [redacted] baseline HDSS score compared with the population in Schollhammer *et al.* 2015.

Limited baseline characteristics were reported in Schollhammer *et al.* 2015 but the EAG notes that Schollhammer *et al.* 2015 comprised a higher proportion of females compared to Hyp-18/2016 Phase3a (56.7% versus 49.1%, respectively) and a lower proportion of males (CS Appendix Table 8). Median age was similar between the two studies (approximately 35 years). Prior treatments were not reported for Schollhammer *et al.* 2015. The EAG also notes that outcome data from Schollhammer *et al.* 2015 used in the company's ITCs are from 6-weeks, whereas the GPB 1% cream data are from 4-weeks (Day 29). There is thus a discrepancy in the timepoint for outcome assessment between the two studies.

The company reported that their decision to use the efficacy results for oxybutynin from Schollhammer *et al.* 2015 to represent the effectiveness of antimuscarinic treatments overall was consistent with the approach taken by Wade *et al.* 2017[11] in the Centre for Reviews and Dissemination Health Technology Assessment, where all oral treatments for hyperhidrosis were grouped as a single category in a network meta-analysis (NMA). Wade *et al.* also reported that their clinical experts considered effectiveness to be broadly similar between oral hyperhidrosis medications.

The EAG notes that the published NMA by Wade *et al.* only incorporates 4-week data for oral medications and these are sourced from Mehrotra *et al.,* which evaluated 2% or 4% unlicensed GPB wipes versus placebo in patients with axillary hyperhidrosis, and Müller *et al.,* which evaluated oral methantheline bromide versus placebo in patients with axillary or palmar hyperhidrosis.[25, 26] These studies are not included in the company ITCs as the treatments are not reflective of those available and used in UK clinical practice; however, the Wade *et al.* NMA was used in a scenario analysis within the company's economic model.

3.4.1.3 Botulinum toxin

The company SLR identified six placebo-controlled studies evaluating the efficacy of botulinum toxin A in patients with severe PAHH. However, only two studies (Lowe *et al.* 2007[22] and Lee *et al.* 2022[27]) reported response using the HDSS. The study by Lee *et al.* was subsequently excluded by the company due to concerns around its applicability to UK clinical practice as it was conducted

exclusively in Korea. The remaining Lowe *et al.* study was based in the USA and used to inform botulinum toxin A in the company's ITCs.

Lowe *et al.* 2007 compared botulinum toxin A 50U per axilla, 75U per axilla, and placebo, in patients with severe PAHH.[22] The study reported the proportion of patients achieving a ≥2-point improvement in HDSS score at 4 weeks after both the first and second treatments with re-treatment not allowed to be sooner than 8 weeks after the previous treatment session. Lowe *et al.* enrolled 322 patients across the three study arms. Mean baseline HDSS score was 3.5, [redacted] (Table 37).

In addition, [redacted], the EAG is concerned that the prior treatments received by patients in Lowe *et al.* are not reflective of the UK patients likely to receive botulinum toxin A. In Lowe *et al.*, prior treatments included high-strength antiperspirants (15%, 44/292); herbal, organic, or plant-based products (9%, 28/318); medications for excessive sweating (18%, 56/319); and iontophoresis (6%, 18/321). The EAG notes that there was a washout period of 24 hours for over-the-counter antiperspirants and 7 days for all other treatments, prior to injection of botulinum toxin A.

Table 37. Baseline characteristics for studies in the company's botulinum toxin A ITCs

Baseline characteristic	Hyp-18/2016 Phase3a FASa	Lowe *et al.* 2007
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: DLQI, Dermatology Life Quality Index; FASa, Full Analysis Set for Phase 3; GPB, glycopyrronium bromide; U, units.

The EAG notes that the company has conducted ITCs using data from Lowe *et al.* for each dose of botulinum toxin A (50 U/axilla) and (75 U/axilla), combining the doses, and also separately using the data from 4 weeks after the first injection and 4 weeks after the second injection. Results are discussed in Section 3.4.3. The EAG notes that the timepoint for outcome assessment in the

botulinum toxin A data used in the ITCs from Lowe *et al.* 2007 is 4-weeks and therefore consistent with the Day 29 data used from Hyp1-18/2016 Phase 3a for GPB 1% cream. However, the EAG also notes that the data for botulinum toxin A are from only a single timepoint of 4 weeks after treatment and therefore do not reflect the expected treatment waning with botulinum toxin A reported by the EAG's clinical expert from approximately month 4 onwards.

The published NMA by Wade *et al.* discussed in Section 3.4.1.2 includes data from Lowe *et al.* 2007 and Ohshima *et al.* 2013[28] for botulinum toxin A versus placebo in patients with axillary hyperhidrosis but Ohshima *et al.* was excluded from the company's SLR because it was published in Japanese. The EAG also notes that Ohshima *et al.* reported outcomes at 3 months, and these were assumed to be comparable to 4-week data within the Wade *et al.* NMA. Data from the Wade *et al.* NMA for botulinum toxin A versus placebo are used in the company ITCs and within a scenario analysis in the company's economic model.

3.4.2 Statistical methods

The Bucher ITC method was used by the company using placebo as the common comparator in all analyses. Bucher ITCs were conducted for GPB 1% cream versus oxybutynin (antimuscarinics), and for GPB 1% cream versus botulinum toxin A.

The ITCs use data for GPB 1% cream from the Hyp-18/2016 Phase 3a study, and data from Schollhammer *et al.* 2015 for antimuscarinics, and from Lowe *et al.* 2007 for botulinum toxin A. In addition, scenario analyses were conducted using the relevant odds ratios (ORs) estimated from the network meta-analysis (NMA) published in Wade *et al.* 2017 for medications (antimuscarinics) vs placebo and botulinum toxin A vs placebo for the HDSS score ≥2 improvement outcome.

Analyses using the Phase 3a GPB 1% cream data are conducted using both the FASa and PPSa populations and analyses of botulinum toxin A include separate analyses for different doses and different time points in the botulinum toxin A study as detailed in Section 3.4.1.3.

The data used in the ITCs are summarised in the CS Tables 12, 14 and 16.

3.4.3 Clinical effectiveness results

The results of the Bucher ITCs for antimuscarinics and botulinum toxin A versus GPB 1% cream are presented in Table 38.

For antimuscarinics compared with GPB 1% cream, the ORs are [redacted] However, as discussed in Section 3.4.1.2, there are differences between the trials in the study populations and the timepoints at which outcomes were measured and therefore the results should be interpreted with caution (**Key issue 4**, Section 1). As noted by the company, these discrepancies likely violate the assumptions required for the Bucher method and contribute to the uncertainty in the estimated treatment effects.

The ORs for botulinum toxin A versus GPB 1% cream are [redacted]. However, as discussed in Section 3.4.1.3, the data for botulinum toxin A in the ITCs (Lowe *et al.* 2007) are from only a single timepoint of 4 weeks and therefore do not reflect the expected treatment waning with botulinum toxin A reported by the EAG's clinical expert from approximately month 4 onwards (**Key issue 4**, Section 1). In addition, the EAG notes that [redacted] and that they should therefore also be interpreted with caution.

Table 38. Results from the company's Bucher ITCs[11, 17, 21, 22] (reproduced from Table 17 of the CS)

#	Treatment	Source of data	Timepoint	HDSS response endpoint	OR (95% CI)
Antimuscarinics vs. GPB 1% cream					
1	GPB 1% cream	FASa	Day 29	≥2	[redacted]
	Antimuscarinics	Schollhammer *et al.* (2015)	6 weeks	≥2	
2	GPB 1% cream	PPSa	Day 29	≥2	[redacted]
	Antimuscarinics	Schollhammer *et al.* (2015)	6 weeks	≥2	
3	GPB 1% cream	FASa	Day 29	≥1	[redacted]
	Antimuscarinics	Schollhammer *et al.* (2015)	6 weeks	≥1	
4	GPB 1% cream	FASa	Day 29	≥2	[redacted]
	Antimuscarinics	Wade *et al.* (2017)	4 weeks	≥2	
Botulinum toxin vs. GPB 1% cream					
4	GPB 1% cream	FASa	Day 29	≥2	[redacted]
	Botulinum toxin 100U	Lowe *et al.* (2007)	4 weeks after initial tx	≥2	
5	GPB 1% cream	FASa	Day 29	≥2	[redacted]
	Botulinum toxin 150U	Lowe *et al.* (2007)	4 weeks after initial tx	≥2	
6	GPB 1% cream	FASa	Day 29	≥2	[redacted]

	Botulinum toxin	Lowe *et al.* (2007)	4 weeks after initial tx	≥2	
7	GPB 1% cream	FASa	Day 29	≥2	[redacted]
	Botulinum toxin 100U	Lowe *et al.* (2007)	4 weeks after second tx	≥2	
8	GPB 1% cream	FASa	Day 29	≥2	[redacted]
	Botulinum toxin 150U	Lowe *et al.* (2007)	4 weeks after second tx	≥2	
9	GPB 1% cream	FASa	Day 29	≥2	[redacted]
	Botulinum toxin	Lowe *et al.* (2007)	4 weeks after second tx	≥2	
10	GPB 1% cream	PPSa	Day 29	≥2	[redacted]
	Botulinum toxin 100U	Lowe *et al.* (2007)	4 weeks after initial tx	≥2	
11	GPB 1% cream	PPSa	Day 29	≥2	[redacted]
	Botulinum toxin 150U	Lowe *et al.* (2007)	4 weeks after initial tx	≥2	
12	GPB 1% cream	PPSa	Day 29	≥2	[redacted]
	Botulinum toxin	Lowe *et al.* (2007)	4 weeks after initial tx	≥2	
13	GPB 1% cream	PPSa	Day 29	≥2	[redacted]
	Botulinum toxin 100U	Lowe *et al.* (2007)	4 weeks after second tx	≥2	
14	GPB 1% cream	PPSa	Day 29	≥2	[redacted]
	Botulinum toxin 150U	Lowe *et al.* (2007)	4 weeks after second tx	≥2	
15	GPB 1% cream	PPSa	Day 29	≥2	[redacted]
	Botulinum toxin	Lowe *et al.* (2007)	4 weeks after second tx	≥2	
16	GPB 1% cream	FASa	Day 29	≥2	[redacted]
	Botulinum-toxin	Wade *et al.* (2017)	4 weeks	≥2	

Abbreviations: CI, confidence interval; FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ITC, indirect treatment comparison; N, number; OR, odds ratio; PPS, per-protocol set; U, units.

3.5 Conclusions of the clinical effectiveness section

The EAG is concerned that the population in the key trial providing clinical evidence on GPB 1% cream (Hyp-18/2016 Phase 3a and 3b trial) does not align with the proposed population in UK clinical practice in terms of prior treatments. The company's proposed positioning of GPB 1% cream is for use after lifestyle advice and topical aluminium chloride preparations, but the EAG notes that inclusion criteria for the Hyp-18/2016 Phase 3a and 3b trials do not appear to specify any requirements regarding prior treatment with topical aluminium chloride preparations. In addition, based on data received in response to the clarification questions, it appears that fewer than 15% of patients in the Hyp-18/2016 Phase 3a and 3b trials had received at least 1 prior hyperhidrosis treatment. The EAG is therefore concerned that the population in the key trial does not align with the company's proposed positioning for GPB 1% cream in the NHS treatment pathway (See Section 2.3). The EAG is particularly concerned that patients who have failed on first-line treatments may potentially be more challenging to treat and so may be less likely to respond to subsequent treatments.

The EAG considers that some amendments to the search strategies in the SLR performed to identify clinical evidence would be useful in terms of improving robustness and reducing the risk of studies being missed, and that more details regarding quality assessment of non-randomised studies could be provided. However, the EAG considers it unlikely that any relevant studies have been missed and notes that non-randomised studies for comparator treatments were not utilised in the clinical section of this appraisal (see Section 3.1).

The intervention specified in the NICE final scope was GPB 1% cream and this reflects the intervention in both the CS and the Hyp-18/2016 Phase 3a and 3b trial.

The EAG notes that patients in the placebo arm of Hyp-18/2016 Phase 3a who entered Phase 3b received GPB 1% cream as needed from the start of Phase 3b (at least twice per week but at most once daily) and were not specifically required to apply the cream daily for the first 4 weeks of treatment (the treatment regimen recommended in the summary of product characteristics for the first 4-weeks). The EAG is unsure what impact this potential discrepancy in treatment may have had (if any) on the overall results of Phase 3b, but notes that the company considers the full effect of the cream would be visible after 4 weeks (week 8 for placebo patients from 3a entering 3b, [redacted] [company response to clarification question A8]). The EAG is therefore concerned about the reliability of the FASb data, and notes that

week 4 data for HDSS from the FASnewb population appear to have been used in the company's economic model with FASb data used for the later timepoints.

The EAG considers that oral anticholinergics are likely to represent the most appropriate comparator for GPB 1% cream in primary care based on the company's proposed positioning and that potential comparators for GPB 1% cream in secondary care are both oral anticholinergics and botulinum toxin A. Given the lack of head-to-head trial data the company has conducted indirect treatment comparisons to provide estimates of effectiveness for GPB 1% cream versus antimuscarinics and GPB 1% cream versus botulinum toxin A and the ITCs are used in the economic model. However, the EAG is concerned about the reliability of the evidence from the company's ITCs.

The EAG also considers there to be a risk of bias given the open-label nature of Phase 3b, particularly for the subjective outcomes such as HDSS change from baseline, which is the key outcome informing the efficacy of GPB 1% cream in the economic model (see Section 3.2).

Absolute change in sweat production was the primary efficacy outcome in Phase 3a and Phase 3b. Absolute reduction in sweat production from baseline to day 29 for Phase 3a FASa in logarithmic values was [redacted] in the GPB 1% cream group compared to the placebo group ([redacted] [Table 32]). [redacted], the absolute reduction in sweat production from baseline to Week 12 for Phase 3b FASnewb in logarithmic values [redacted] [see Section 3.3.1]).

[redacted]

[redacted]

In terms of safety, on review of the trial data and clinical expert feedback, while there may be some differences between treatments in terms of the profile of AEs that may be experienced, [redacted] that will likely not receive a specific treatment, with dose interruptions or reductions more likely, and comparisons between treatments is limited given the differences in study design, trial duration and sample size (see Section 3.3.4).

The EAG notes that the company's economic model includes AEs for GPB 1% cream informed by data from Phase 3b of the Hyp1-18/2016 trial with AEs for the comparator treatments informed by data from the studies used to perform ITCs against GPB 1% cream for the HDSS outcome, including Schollhammer *et al.* 2015 for oral antimuscarinics and Lowe *et al.* 2007 for botulinum toxin A. However, based on feedback received from the EAG's clinical expert and the statement within the [redacted], the EAG prefers the exclusion of AEs completely from its base case (see Section 4.2.5.1).

The company conducted Bucher ITCs for antimuscarinics and botulinum toxin A versus GPB 1% cream, but the EAG has concerns about the reliability and generalisability of the results from these analyses (see Section 3.4). For antimuscarinics compared with GPB 1% cream, the ORs are [redacted] However, the EAG considers the results should be interpreted with caution due to the differences in the study populations and the timepoints at which outcomes were measured. As noted by the company, these discrepancies likely violate the assumptions required for the Bucher method and contribute to the uncertainty in the estimated treatment effects. The EAG considers that the use of alternative more complex indirect treatment comparison methods could potentially help to resolve some of the underlying differences between the trial populations in the comparator studies and the GPB 1% cream trial. However, the trial population for antimuscarinics does not fully align with the marketing authorisation population for GPB 1% cream in terms of patients with severe axillary hyperhidrosis and the prior treatments in the botulinum toxin A trial are not fully reflective of UK clinical practice, therefore the EAG also considers that further indirect treatment comparisons would not fully address the current uncertainties in the clinical evidence.

The ORs from the ITCs for botulinum toxin A versus GPB 1% cream are [redacted]. However, the Lowe *et al.* 2007 data for botulinum toxin A in the ITCs are from only a single timepoint of 4 weeks and therefore do not reflect the expected treatment waning with botulinum toxin A reported by the EAG's clinical expert from approximately month 4 onwards. In addition, the EAG notes that [redacted]. The EAG thus considers the results of these ITCs subject to [redacted] and that they should therefore also be interpreted with caution.

The EAG notes that the Wade *et al.* NMA was used in a scenario analysis within the company's economic model but considers this also to have limitations due to differences in the treatments included in the antimuscarinics studies and differences in the populations and timing of outcome assessment in the botulinum toxin A studies. The EAG therefore also recommends caution in drawing conclusions from the results of the analyses including data from the Wade *et al.* NMA.

4 Cost effectiveness

This section presents a summary and critique of the cost-effectiveness evidence included in the company's submission. Section 4.1 focuses on the company's review of the cost-effectiveness evidence and section 4.2 covers the company's economic evaluation.

The results of the company's updated base case analysis post factual accuracy check (FAC) for the comparison with oral antimuscarinics and botulinum toxin A are presented in Table 39 and Table 40, respectively.

The company's base case fully incremental analysis results in antimuscarinics being dominated by GPB 1% cream and the results for botulinum toxin A are the same as in the pairwise comparison of GPB 1% cream versus botulinum toxin A, as shown in Table 40.

Table 39. Company's updated base case results (post FAC) versus oral antimuscarinics

Interventions	Total Costs (£)	Total LY*	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Antimuscarinics	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Probabilistic results							
Antimuscarinics	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: FAC, factual accuracy check; GPB, Glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

*Undiscounted

Table 40. Company's updated base case results (post FAC) versus botulinum toxin A

Interventions	Total Costs (£)	Total LY*	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Probabilistic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Interventions	Total Costs (£)	Total LY*	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							

Abbreviations: FAC, factual accuracy check; GPB, Glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

*Undiscounted

4.1 Critique of the review of cost effectiveness evidence

The company conducted a systematic literature review (SLR) to identify published cost-effectiveness, health-related quality of life (HRQoL), and cost and resource use evidence for treatments used in the management of patients with hyperhidrosis. The company's SLR was conducted in March 2025. A summary of the External Assessment Group (EAG)'s critique of the methods implemented by the company to identify relevant evidence is presented in Table 41.

Table 41. Summary of the company's economic systematic literature review

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix E.1.2	Appendix E.1.2	Appendix E.1.2	Appropriate. The EAG considers that keeping the search strategy broad for all evidence related to hyperhidrosis is more likely to capture studies which include primary axillary hyperhidrosis as a subgroup.
Inclusion/ exclusion criteria	Appendix E.1.3.1	Appendix E.1.3.1	Appendix E.1.3.1	Appropriate. The company specified an exclusion criterion of <50% of adult patients with primary or secondary hyperhidrosis, which the EAG considers is appropriate to capture relevant evidence for the population of interest for this topic.
Screening	Appendix E.1.3	Appendix E.1.3	Appendix E.1.3	Appropriate.
Data extraction	Appendix E.1.3.2	Appendix E.1.3.2	Appendix E.1.3.2	Appropriate.
Quality assessment of included studies	Appendix E.1.3.2	Appendix E.1.3.2	Appendix E.1.3.2	Appropriate.

Abbreviations: CS, company submission; EAG, External Assessment Group; HRQoL, health-related quality of life.

Overall, a total of six cost-effectiveness papers reporting on four unique studies, three HRQoL studies and six resource and cost use papers were identified by the SLR.

Of the four unique cost-effectiveness studies identified, the company relied on two of the studies (also included as part of the resource use and costs SLR) to inform several assumptions included in their own *de novo* economic model:

- A systematic review and value-of-information analysis Health Technology Assessment (HTA) monograph (Wade *et al*. 2017) of interventions for hyperhidrosis in secondary care.[11]
- A cost-effectiveness analysis of topical glycopyrronium tosylate for primary axillary hyperhidrosis (PAHH) (Bloudek *et al*. 2021).[29]

A study by Kamudoni *et al*. 2014, identified in the HRQoL systematic literature review, provided EQ-5D health state utility values stratified by HDSS score. These values were subsequently incorporated into both the HTA monograph (Wade *et al*. 2017) and Bloudek *et al*. 2021, and ultimately used to inform the company's base case utility values in their economic model.[11, 29, 30]

The EAG considers the company's SLR was robust and identified relevant studies for the appraisal. Section 4.2 describes in detail the assumptions in the company's economic model that have been informed by studies identified in the SLR.

4.2 Critique of the submitted economic evaluation

4.2.1 NICE reference case checklist

Table 42 summarises the EAG's assessment of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.

Table 42. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Adheres to the reference case.
Perspective on costs	NHS and PSS	Adheres to the reference case.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Adheres to the reference case.

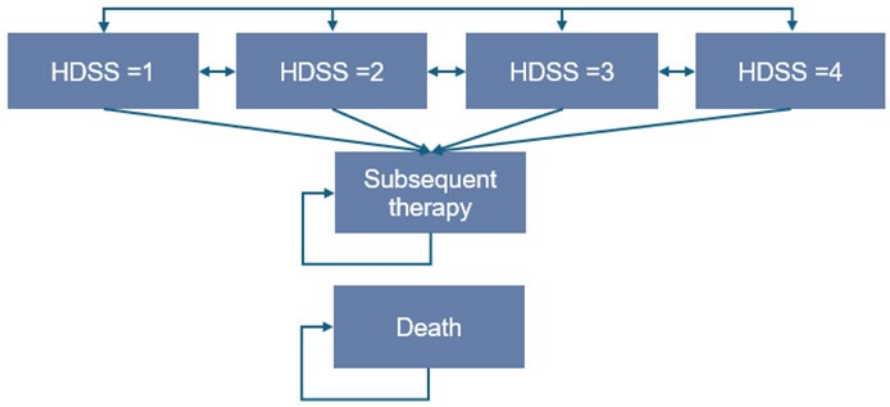
Element of health technology assessment	Reference case	EAG comment on company's submission
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Lifetime. The EAG considers that a shorter time horizon may be more appropriate as no difference in mortality is assumed and approximately 20 years of the model's estimates account for subsequent treatment costs without corresponding treatment benefits. Based on advice from its clinical experts, the EAG considers a shorter time horizon is likely to capture all important differences in costs and outcomes between treatments and would still adhere to the NICE reference case.
Synthesis of evidence on health effects	Based on systematic review	Adheres to the reference case.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Adheres to the reference case.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Published EQ-5D-5L data obtained from USA and UK patients with primary hyperhidrosis. Utility values were not mapped to EQ-5D-3L, as per the reference case.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The EAG considers there is uncertainty as to whether the published EQ-5D-5L values are representative of the UK population with PAHH, as the majority of patients included in the source study were from the USA.[30, 31]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Adheres to the reference case.
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	Adheres to the reference case.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Adheres to the reference case.

Element of health technology assessment	Reference case	EAG comment on company's submission
Abbreviations: EAG, External Assessment Group; NHS, national health service; PAHH, primary axillary hyperhidrosis; PSS, personal social services; QALY, quality adjusted life year		

4.2.2 *Modelling approach and model structure*

A single, Markov model was developed in Microsoft Excel© to assess the cost-effectiveness of GPB 1% cream for treating severe PAHH in adults. The economic model features six health states: four based on the Hyperhidrosis Disease Severity Scale (HDSS) score (1-4), a subsequent therapy state, and death. Previous published models for PAHH similarly utilised the HDSS score as the primary treatment response outcome.[11, 29, 32] Figure 4 presents the company's model schematic.

Figure 4. Company's model structure (reproduced from Figure 9 of the CS)



Abbreviations: CS, company submission; HDSS, Hyperhidrosis Disease Severity Scale

Patients enter the model in one of the HDSS health states, determined by their baseline HDSS score derived from the Hyp1-18/2016 Phase 3b trial of GPB 1% cream (see Section 2.3.1). While on treatment with GPB 1% cream, oral antimuscarinics or botulinum toxin A, patients can move between the HDSS health states based on response to treatment or die. Response to treatment is informed by Hyp1-18/2016 Phase 3b for GPB 1% cream and odds ratios (ORs) from the indirect treatment comparison for oral antimuscarinics and botulinum toxin A (see Section 4.2.3 for further details). If patients lose response to treatment or discontinue treatment for any other reason, they transition to the subsequent therapy health state where they are assigned a basket of next-line treatments and return to their baseline HDSS score. Patients remain in the subsequent therapy health state until death.

The company has assumed no excess mortality from severe PAHH. Thus, transitions to death are informed by background mortality, estimated using ONS lifetables (2021-2023) adjusted for age and sex.[33]

A model cycle length of two weeks, with half cycle correction, was implemented in the model, aligned with reporting timepoints in Hyp1-18/2016 Phase 3b. The model time horizon was set to 65 years (lifetime). The perspective of the analysis is based on the UK National Health Service (NHS), with costs and benefits discounted using a rate of 3.5% as per the NICE reference case.

4.2.2.1 EAG critique

In Figure 2 of the company submission (CS), the proposed position of GPB 1% cream is:

- As an alternative to oral anticholinergic medication (antimuscarinics) in primary care.
- Prior to oral anticholinergic medication (antimuscarinics) and botulinum toxin type A in secondary care.

However, the economic model does not make a distinction between healthcare settings, instead implementing proportions of the type of care setting used for administration and monitoring of patients on GPB 1% cream and the comparators (Table 40 of the CS), described further in Section 4.2.7.3. The company has assumed that GPB 1% cream is only administered in a primary care setting, which contradicts Figure 2 of the CS (**Key issue 2**, Section 1).

During the clarification stage, the EAG requested further explanation from the company regarding the position of GPB 1% cream in the treatment pathway. The company explained that in the long-term, GPB 1% cream is expected to be used only in primary care as an alternative to anticholinergics. The company considered that there is a prevalent population in secondary care who would also be eligible for treatment with GPB 1% cream and have stated that they expect it will displace the use of oral antimuscarinics and botulinum toxin A.

Given the company's proposed position of GPB 1% cream, the EAG recommended the company to provide two separate models to reflect the primary care and secondary care positions of GPB 1% cream, as the company's base case approach means that the fully incremental analysis is uninterpretable. Based on information from its clinical experts, the EAG considers that the main comparator for the primary care model would be propantheline bromide as it is the only treatment with marketing authorisation for PAHH and would be predominantly prescribed by GPs. For the

secondary care model, the EAG's clinical expert considers that the comparators would be modified-release oxybutynin 5mg once daily and botulinum toxin A.

Rather than update their base case, the company provided scenarios reflecting the primary care and secondary care approaches recommended by the EAG and results are presented in Section 5.1.1.2. The EAG considers that the distinction based on care setting should be applied to the cost-effectiveness results and therefore, presents its preferred assumptions by primary care and secondary care setting, with the comparators as recommended by the EAG's clinical expert. The EAG's preferred assumptions are presented in Section 5.2.3.

The EAG considers that the model's lifetime horizon may be excessive, given the nature of the condition and the treatments under consideration (**Key issue 6**, Section 1). In the NICE manual, it states, "*a time horizon shorter than a patient's lifetime could be justified if there is no differential mortality effect between technologies and the differences in costs and clinical outcomes relate to a relatively short period*".[34]

For the company's base, no difference in mortality is assumed (see Section 4.2.4). With regards to costs and clinical outcomes, the EAG's clinical expert advised that treatment response typically becomes clear within the first month, allowing non-responders to quickly transition to alternative therapies. Furthermore, the EAG's clinical expert considered that within two years, most patients are expected to have identified an effective treatment and are likely to remain on it long-term. In the study by Wade *et al.* 2017 hyperhidrosis was assumed to spontaneously resolve after the age of 65 years based on advice from clinical experts[11] and the EAG's clinical expert confirmed that they do not often see patients over the age of 50 years.

Additionally, patients spend the majority of the model time horizon in the subsequent treatment health state. Patients on GPB 1% cream spend approximately [redacted] years out the 65 years of the model time horizon in the subsequent treatment health state. For patients in the comparator arms of the model, approximately [redacted] years are spent in the subsequent treatment health state.

Consequently, the EAG considers that a lifetime horizon may introduce unnecessary "noise" into the results, particularly because, in the company's model, patients incur the costs of subsequent treatment without corresponding treatment benefits. This is based on the company's base-case assumption that patients return to their baseline HDSS score upon treatment discontinuation and initiation of subsequent therapy, which the EAG's clinical expert considers clinically implausible.

Instead, a shorter time horizon may be appropriate to capture all important differences in costs and outcomes between treatments and would still adhere to the NICE reference case.

During the clarification stage, the EAG requested, and the company provided, scenarios exploring a time horizon of 72 weeks to reflect the observed follow-up period from Hyp1-18/2016 Phase 3b and a time horizon of two years, which aligned with the EAG's clinical expert's view that the most clinically important differences between treatments would be captured. Results of the scenarios are presented in Section 5.1.1.2. The EAG considers that a two-year time horizon may be more appropriate to capture the important costs and benefits of each treatment and has implemented this with its preferred assumptions (Section 5.2.3).

With regards to the subsequent treatment health state, as mentioned earlier, the company has assumed that patients return to their baseline HDSS score upon treatment discontinuation and initiation of subsequent therapy. In the company's base case, patients on comparator treatments discontinue treatment sooner than with GPB 1% cream. As such, the assumption of patients on subsequent treatment returning to their baseline HDSS score is potentially biased against the comparators (Section 4.2.7.5). Instead, the EAG considers that the subsequent treatment health state could have been modelled in the same way as initial treatment, i.e. based on the four HDSS health states and that it would have been a more accurate way to capture the subsequent treatment costs and benefits.

The company stated that more complex methods for modelling subsequent treatments were explored such as using a payoff method but considered there was a lack of robust data available to support this modelling approach. Additionally, the company considered that if patients had failed second-line treatment, their underlying PAHH may be more difficult to treat and as such are unlikely to experience the same level of benefit as patients who are treated earlier, but are expected to incur the costs of treatment. This issue is explored further in Section 4.2.8.

4.2.3 Treatment effectiveness

4.2.3.1 GPB 1% cream

Improvement in HDSS score for GPB 1% cream is informed by data from the full analysis set (FAS) of the Hyp1-18/2016 Phase 3b trial. Table 43 presents the number of patients with a ≥2, ≥1 and 1-2 points improvement in the HDSS score up to week 72. The EAG notes that outcome data for week 4 is informed only by the new recruit cohort of Hyp1-18/2016 Phase 3b and data from week 8 to week

72 is informed by the new recruit cohort and the rollover patients (both GPB 1 % cream and placebo cohorts) from Hyp1-18/2016 Phase 3a.

Table 43. Improvement in HDSS score from the FAS population of Hyp1-18/2016 Phase 3b (reproduced from Table 26 of the CS)

Week	≥2			≥1			1 or 2		
	n	N	%	n	N	%	n	N	%
4	[redacted]								
8									
12									
28									
52									
72									

Abbreviations: CS, company submission; FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Scale; N, number of patients.

The data presented in Table 43 were used to estimated transition probabilities of achieving a 1-, 2- or 3-point improvement in HDSS score at weeks 4, 8, 12, 28, 52 and 72 for patients in the GPB 1% cream arm of the model. After week 72, the company assumed that there are no further transitions between HDSS health states for GPB 1% cream. Transition probabilities included in the model for GPB 1% cream are presented in Table 28 of the CS.

As the model cycle length is two weeks, between the timepoints of the transition probabilities the company linearly increased the proportion occupying each HDSS health state until the next time point for the transition probability. For example, at week 4, the proportion occupying the HDSS 2 health state is [redacted] and at week 8 it is [redacted]. To work out the week 6 proportion, the company divided the difference in proportions between the two timepoints and distributed this among the number model cycles between the two timepoints ([redacted], week 6 proportion is therefore [redacted]).

4.2.3.2 Comparators

The company performed a Bucher indirect treatment comparison (ITC), described in Section 3.4, to estimate the comparative effectiveness of oral antimuscarinics and botulinum toxin A versus GPB 1% cream. The company was able to estimate ORs for ≥2 point improvement and ≥1 point improvement in the HDSS score for oral antimuscarinics and ≥2 point improvement in the HDSS score for botulinum toxin A (see Table 44). The ORs for oral antimuscarinics and botulinum toxin A indicate

that both treatments are [redacted].

The company made several assumptions around comparator effectiveness in the model and these are as follows:

- Data were unavailable for 1–2-point improvement in the HDSS score for oral antimuscarinics. Instead, the company used OR for the ≥1 point improvement in the HDSS score to estimate the 1–2-point HDSS improvement for oral antimuscarinics.
- Data were unavailable for ≥1 point improvement and 1–2-point improvement in the HDSS score for botulinum toxin A. Instead, the company estimated the proportional difference between the ORs for the ≥2 point improvement and ≥1 point improvement in the HDSS score for oral antimuscarinics and used this to estimate the ORs for the ≥1 point improvement and 1–2-point improvement in the HDSS score for botulinum toxin A.
- The company assumed that botulinum toxin A treatment is given every six months and the time to maximum effectiveness is four weeks after treatment. From week 4 to week 26, the company assumed botulinum toxin A treatment effectiveness wanes linearly until patients return to their baseline HDSS score.
- Aligned with the approach for GPB 1% cream, the company assumed no change in HDSS health states for patients remaining on oral antimuscarinic treatment after 72 weeks in the model.

Table 44. Comparator treatment effectiveness estimates included in the model

Treatment	Improvement in HDSS score	Odds ratio vs GPB 1% cream (95% CI)	Source/ assumption
Oral antimuscarinics	≥2	[redacted]	Bucher ITC
	≥1	[redacted]	Bucher ITC
	1-2	[redacted]	Assumed to be the same as the OR for ≥1 point improvement in the HDSS score.
Botulinum toxin A	≥2	[redacted]	Bucher ITC
	≥1	[redacted]	Estimated based on the proportional difference between the ORs for the ≥2 point improvement and ≥1 point improvement in the HDSS score for oral antimuscarinics
	1-2	[redacted]	

Abbreviations: CI, confidence interval; GPB, glycopyrronium bromide; ITC, indirect treatment comparison; HDSS, Hyperhidrosis Disease Severity Scale; OR, odds ratio;

The company applied the ORs to the data on improvement in HDSS score for GPB 1% cream from Hyp1-18/2016 Phase 3b (Table 43) to estimate equivalent data for the comparators (Table 45), which were then used to estimate transition probabilities in the model (presented in Appendix 7.3).

Table 45. Estimated improvement in HDSS score for oral antimuscarinics and botulinum toxin A, compared to GPB 1% cream included in the model

Week	≥2			≥1			1 or 2		
	GPB 1% cream	Oral AMSC	BTX	GPB 1% cream	Oral AMSC	BTX	GPB 1% cream	Oral AMSC	BTX
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AMSC, antimuscarinics; CS, company submission; BTX, botulinum toxin A; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale.

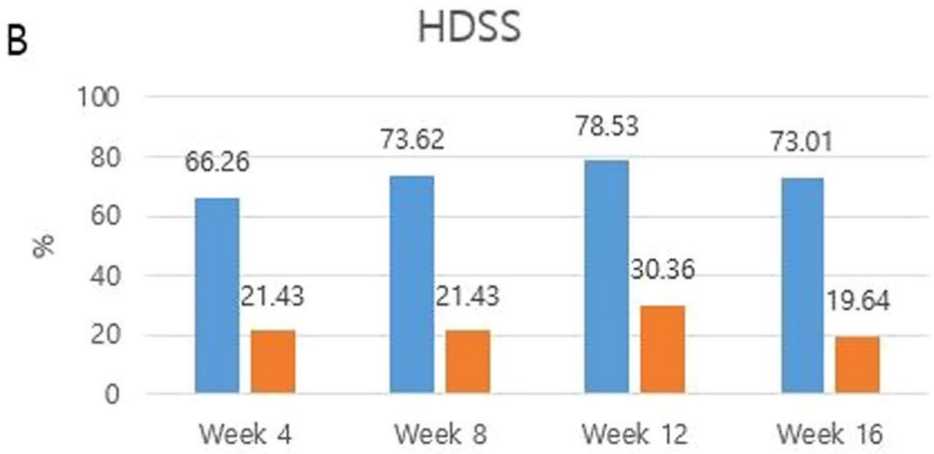
4.2.3.3 EAG critique

Generally, the EAG considers the company's approach to treatment effectiveness in the model is appropriate. However, there are some key assumptions that have been made, which the EAG considers are a source of uncertainty. As described earlier, the company has assumed that the time to maximum effectiveness for botulinum toxin A is four weeks after treatment. In the company's model, from week 4 to week 26, botulinum toxin A treatment effectiveness wanes linearly until patients return to their baseline HDSS score (**Key issue 7**, Section 1). The EAG's clinical expert advised that botulinum toxin A is one of the most effective treatments for severe PAHH and that patients would see a clinically significant reduction in sweating and improvement in quality of life within one week of treatment and this would be maintained up to month 4. The EAG's clinical expert considered that the company's base case assumption of treatment waning from week 4 for botulinum toxin A was clinically implausible.

In their clarification response, the company provided some evidence from a study by Heckmann *et al*. 2005, which suggested that treatment effectiveness after the second administration of botulinum toxin A declines from week 2, based on gravimetric measurement of sweat production and patient self-assessment.[35] However, the outcome of interest of the study does not align with HDSS used in

the company's model. A more recent study (Lee *et al*. 2022) found that at week 12 after treatment, peak efficacy as measured by HDSS was observed (Figure 5).[27]

Figure 5. Symptom Improvement based on Hyperhidrosis Disease Severity Scale (HDSS), Lee *et al.* 2022[27]



The EAG notes that only one botulinum toxin A treatment was given in the study and follow-up was 16 weeks, so the long-term trend was unclear. However, the EAG considers that based on the Lee *et al*. study, there was only an approximately 5% difference in HDSS score between week 8 and 12 and week 12 and 16, suggesting that treatment effectiveness for botulinum toxin A was relatively stable.

In their clarification response, the company provided a scenario where the treatment effectiveness of botulinum toxin A wanes after week 16 until week 26 (next administration of botulinum toxin A). The results of the scenario are presented in Section 5.1.1.2 and included as part of the EAG's preferred assumptions, presented in Section 5.2.3.

The EAG was concerned with the company's assumption that the proportional difference between the ORs for the ≥2 point improvement and ≥1 point improvement in the HDSS score for oral antimuscarinics was used to estimate the ORs for the ≥1 point improvement and 1–2-point improvement in the HDSS score for botulinum toxin A. No evidence was supplied by the company to suggest that the relationship between achieving a ≥1 point versus ≥2 point improvement in the HDSS score was consistent for both treatments. The company provided a scenario in the CS that assumed the botulinum toxin A OR for ≥1-point improvement in the HDSS score was the same as that for ≥2-point improvement and the EAG prefers this assumption as it based on observed data for a related outcome. In their clarification response, the company acknowledges, and the EAG agrees, that the

botulinum toxin A OR for ≥1-point HDSS improvement in the HDSS score is not a key driver of cost-effectiveness. Nonetheless, for completeness, the EAG includes this scenario as part of its preferred assumptions, presented in Section 5.2.3.

Lastly, after week 72 in the model, the company has assumed no change in HDSS score for patients on GPB 1% cream and oral antimuscarinics based on lack of available data beyond that time point. Due to the lifetime horizon of the model, this assumption is applied for 1,644 model cycles (over 63 years) and only the discontinuation rate of each treatment and background mortality results in patients moving out of their week 72 HDSS health state to the subsequent treatment health state or death. However, as mentioned in Section 4.2.2.1, the EAG considers that a shorter time horizon may be more appropriate, especially as it limits the uncertainty around the assumption of no change in HDSS score after week 72 for GPB 1% cream and oral antimuscarinics.

4.2.4 Mortality

The company considered that severe PAHH is not expected to impact on patient mortality. As such, background mortality is applied equally to all arms of the model and is based on ONS lifetables (2021-2023) adjusted for age and sex.[33]

4.2.4.1 EAG critique

The EAG considers the company's approach is appropriate, but based on guidance in NICE DSU TSD 23, the ONS lifetables from 2017-2019 should be used due to the uncertainty about the long-term impact of COVID-19 on the data.[36] During the clarification stage, the EAG requested that the company update the model to use the ONS lifetables from 2017-2019, but instead they provided a scenario. As such, the EAG has included the ONS lifetables from 2017-2019 as part of its preferred assumptions, presented in Section 5.2.3.

4.2.5 Adverse Events

Table 46 presents the adverse events (AEs) that are included in the model for GPB 1% cream, oral antimuscarinics and botulinum toxin A. To align with the model cycle, the company estimated two-week probabilities of AEs, and these are presented in Table 33 of the CS.

In the company's base-case analysis, adverse drug reactions (ADRs) occurring in at least 2% of the safety analysis set from Hyp1-18/2016 Phase 3b (baseline to week 72) were included in the model. The company described ADRs as treatment-emergent adverse events (TEAEs) with an onset on or

after the first application of GPB 1% cream. The EAG notes that in the clinical study report (CSR) for Hyp1-18/2016, it is stated that [redacted].

Adverse events for oral antimuscarinics were based on side-effect data reported for oxybutynin in the study by Schollhammer *et al*. 2015.[21] The company assumed an anticholinergic drug class effect for propantheline bromide, oxybutynin and oral GPB. The EAG notes that in the study by Schollhammer *et al*., 2015 no serious adverse events were reported, no patients discontinued treatment because of side effects and a maximum dose of 7.5 mg of oxybutynin was used in the study to avoid side effects.[21]

For botulinum toxin A, AE data were obtained from the study by Lowe *et al*. 2007.[22] For the company's base case, AE data with an incidence of at least 2% associated with 100U dose of botulinum toxin A was used to align with the dose assumed in the model. The company provided a scenario using 150U dose of botulinum toxin A and included the AEs associated with the higher dose. However, in the Lowe *et al*. study, it was noted that there were no serious treatment-related AEs and no subjects discontinued the study because of treatment-related AEs.[22]

The company acknowledged several "between study" differences in the AE data included in the model. Most notably, duration of observation of AEs was different between studies, with the data for GPB 1% cream based on 72 weeks of data, versus 6 weeks for oral antimuscarinics and 52 weeks for botulinum toxin A.[21, 22] Additionally, while all three studies reported that none of the AEs were serious in nature, there was no other breakdown of low or moderate severity to compare against for each treatment.

Table 46. Adverse events included in the model (reproduced from Table 32 of the CS).

Adverse event	GPB 1% cream (N = 518)		Oral antimuscarinics[21] (N = 30)		Botulinum toxin A 100U[22] (N = 104)	
	n	%	n	%	n	%
Dry eye	[redacted]	[redacted]	0	0.0%	0	0.0%
Dry mouth	[redacted]	[redacted]	13	43.3%	0	0.0%
Application site erythema/flush	[redacted]	[redacted]	1	3.3%	0	0.0%
Application site pruritus	[redacted]	[redacted]	0	0.0%	0	0.0%
Headache	[redacted]	[redacted]	1	3.3%	0	0.0%

Adverse event	GPB 1% cream (N = 518)		Oral antimuscarinics[21] (N = 30)		Botulinum toxin A 100U[22] (N = 104)	
	n	%	n	%	n	%
Nausea	[redacted]	[redacted]	1	3.3%	0	0.0%
Diarrhoea	[redacted]	[redacted]	1	3.3%	0	0.0%
Gastro-oesophageal reflux/other GI disorders	[redacted]	[redacted]	1	3.3%	0	0.0%
Asthenia/Somnolence	[redacted]	[redacted]	1	3.3%	0	0.0%
Dizziness	[redacted]	[redacted]	1	3.3%	0	0.0%
Blurred vision	[redacted]	[redacted]	4	13.3%	0	0.0%
Urinary difficulty/other renal or urinary disorder	[redacted]	[redacted]	1	3.3%	0	0.0%
Injection site pain*	N/A	N/A	N/A	N/A	9	12.5%
Injection site bleeding*	N/A	N/A	N/A	N/A	6	5.8%
Non-axillary sweating/hyperhidrosis*	[redacted]	[redacted]	0	0.0%	6	10.6%

Abbreviations: CS, company submission; GI, gastrointestinal; GPB, glycopyrronium bromide; U, units; N/A, not applicable.

* In the CS, Table 32 and in the economic model, the company report the values for the 75U botulinum toxin A dose rather than the 50U dose. Values reported in this table reflect the 50U botulinum toxin A dose from Lowe *et al*., 2007.[22]

Estimation of the disutility and costs associated with AEs can be found in Section 4.2.6.1 and 4.2.7.7. The duration of each AE was assumed to one model cycle (two weeks), except for injection site pain and bleeding, which was assumed to last 2.4 days as reported in Lowe *et al*. 2007.[22]

4.2.5.1 EAG critique

As described earlier, [redacted] or the comparator studies.[21, 22] Notably, in the study by Schollhammer *et* al. 2015, the authors stated a dose of 7.5 mg of oxybutynin was used to limit side effects, which can be dose dependent.[21] Typically, for cost-effectiveness analyses, only AEs that have a significant cost and HRQoL burden are considered in the economic model (**Key issue 8**, Section 1). For most of the AEs, the company assumed that treatment would incur the cost of a GP appointment plus 10 minutes of pharmacist time (see Section 4.2.7.8).

However, the EAG's clinical expert advised that the AEs included in the economic model would not be severe enough to be treated. Instead, via patient monitoring, AEs would be managed through dose reductions or treatment discontinuation. Both patient monitoring and treatment discontinuation are already included in the model.

The EAG's clinical expert view is aligned with the approach taken in Wade *et al*. 2017, which did not include the impact of AEs for medications or botulinum toxin A in the analysis. As such, the EAG considers that it is appropriate to exclude the impact of AEs from the model as the data are based on mild/moderate events, which are unlikely to have a significant cost and HRQoL. Additionally, the consequences of these less severe AEs, such as the cost of monitoring patients and treatment discontinuation, are already captured in the model.

During the clarification stage, the EAG requested the company to supply a scenario, where AEs for all treatments are excluded from the model, but the company declined to conduct the analysis. The company stated that the tolerability of treatments impacts patient experience and adherence, but they also acknowledged that AEs included in the model are not severe, costs assumed are minimal and can be managed with dose reductions or discontinuation of treatment but can have a meaningful impact on HRQoL.

The EAG considers the company's reason for keeping the impact of AEs in the model is not sufficiently justified and so ran a scenario excluding AEs from the model, and results are reported in Section 5.2.2. The EAG's scenario has also been included as part of the EAG's preferred assumptions, presented in Section 5.2.3.

It should be noted that in the CS, Table 32 and in the economic model, the company reported the AE values for the 75U botulinum toxin A dose rather than the 50U dose from Lowe *et al*. 2007, which the EAG has corrected, with updated base case results reported in Section 5.2.1.

4.2.6 Health-related quality of life

In the Hyp1-18/2016 Phase 3b trial, EQ-5D data were not collected and instead quality of life was measured using the Dermatology Life Quality Index (DLQI). Please refer to Section 3.3.3 for more details on DLQI observed in the trial. Even though a mapping algorithm for DLQI to EQ-5D exists, the company chose not to conduct this analysis. During clarification, the EAG requested that the company undertake a mapping analysis to estimate utility values but the company responded that they would have to formally request access to individual patient level (IPD) data from the data holder and so this was not conducted. The company further justified their decision to not undertake the mapping by stating that the available mapping algorithms were developed on broader dermatology populations and may not be fully reflective of the PAHH population.

Instead, the company's SLR (described in Section 4.1) identified relevant EQ-5D utility values for their base case analysis from a study by Kamudoni *et al*. 2014.[30] This study estimated the burden of primary hyperhidrosis, including health utilities, based on baseline data from patients recruited through online social networking communities and reported EQ-5D-5L utility values by HDSS score.[30] The company stated that the EQ-5D values reported in Kamudoni *et al.* were also used in the cost-effectiveness analyses conducted by Wade *et al*. and Bloudek *et al*.[11, 29, 30] Table 47 presents the company's base health state utility values. It should be noted that the utility value for HDSS=1 health state is based on general population values adjusted for age and sex and this is consistent with Wade *et al*. and Bloudek *et al*.[11, 29] General population utility values were obtained from the HSE 2014 dataset, as recommended by the DSU.[37]

Table 47. Health state utility values included in the model

Health state	Utility value	Source
HDSS=1	0.90	General population values adjusted for age and sex obtained from the HSE 2014 dataset.[37]
HDSS=2	0.85	Kamudoni *et al*. 2014.[30]
HDSS=3	0.80	
HDSS=4	0.69	

Abbreviations: HDSS, Hyperhidrosis Disease Severity Scale.

The company assumed upon entry to the subsequent therapy health state, patients revert back to their baseline HDSS scores and accumulate the utility values associated with the scores.

Utilities in the model were adjusted for age, as per the NICE manual.[34] General population utility values for females adjusted for age were obtained from the HSE 2014 dataset, as recommended by the DSU.[37, 38]

4.2.6.1 Adverse event disutility values

Table 48 outlines the disutility associated with each AE included in the model and their source. See Section 4.2.5 for the AE inclusion criteria in the economic model, AE incidence and duration for the intervention and comparators. The per model cycle AE disutility impact for each treatment arm is [redacted] for GPB 1% cream, -0.00388 for oral antimuscarinics and -0.00028 for botulinum toxin A. The total AE disutility impact over the lifetime horizon of the model for each treatment arm is [redacted] for GPB 1% cream, -0.00263 for oral antimuscarinics and -0.00035 for botulinum toxin A.

Table 48. Adverse event disutility values included in the model (reproduced from Table 34 of the CS)

Adverse event	Disutility	Source
Dry eye	-0.00916	Other eye disorders, Sullivan *et al*. 2011.[39]
Dry mouth	-0.00235	Assumed other inflammatory condition of the skin, Sullivan *et al*. 2011.[39]
Application site erythema/flush	-0.00058	Other skin disorders, Sullivan *et al*. 2011, NICE TA986.[39, 40]
Application site pruritus	-0.00058	Other skin disorders, Sullivan *et al*. 2011, NICE TA986.[39, 40]
Headache	-0.02657	Headache, Sullivan *et al*. 2011, NICE TA935.[39, 41]
Nausea	-0.05120	Other gastrointestinal disorders, Sullivan *et al*. 2011.[39]
Diarrhoea	-0.05120	Other gastrointestinal disorders, Sullivan *et al*. 2011, NICE TA935.[39, 41]
Gastro-oesophageal reflux/other GI disorders	-0.07255	Non-infectious gastroenteritis, Sullivan *et al*. 2011, NICE TA935.[39, 41]
Asthenia/Somnolence	-0.02000	Assumed deficiency and other anaemia, Sullivan *et al*. 2011.[39]
Dizziness	-0.02657	Assumed headache, Sullivan *et al*. 2011, NICE TA935.[39, 41]
Blurred vision	-0.000000000216	Blindness and vision defects, Sullivan *et al*. 2011.[39]
Urinary difficulty/other renal or urinary disorder	-0.07035	Other diseases of bladder and urethra, Sullivan *et al*. 2011.[39]
Injection site pain	-0.00400	Zimmerman *et al*. 2018, NICE TA986.[40, 42]
Injection site bleeding	-0.00400	Zimmerman *et al*. 2018, NICE TA986.[40, 42]
Non-axillary sweating/hyperhidrosis	-0.12182	Assumption. Based on the average disutilities of HDSS health states 2-4 relative to HDSS 1.

Abbreviations: CS, company submission; GI, gastro-intestinal; HDSS, Hyperhidrosis Disease Severity Scale.

4.2.6.2 EAG critique

As noted in Section 4.2.6, the company did not provide the requested trial collected DLQI data mapped to EQ-5D. When EQ-5D data are not available from the relevant clinical trials, the NICE reference case stipulates that EQ-5D data can be sourced from the literature or mapped from other HRQoL measures collected in the trial. While the company used values sourced from the literature, which have also been used in previous cost-effectiveness analyses,[11, 29] the EAG has concerns with the appropriateness of the analysis and resulting utility values (**Key issue 5**, Section 1). Firstly, the publication is over 10 years old and provided in abstract form only. Although the abstract appears to be based on a published thesis,[31] the exact values provided in the abstract are not available in the

full thesis to cross-check. However, as noted in Wade *et al.*,[11] it is likely that this analysis is based on Chapter 8 of the thesis, in which it demonstrates that EQ-5D data have been collected from both USA and UK patients, with the majority being from the USA. It is not clear from the information provided if the resulting EQ-5D utilities have been valued using the USA or UK value set. As the NICE reference case requires that a representative sample of the UK population is used in the valuation of health-related quality of life measurements to produce utility values, this adds further uncertainty into the appropriateness of the values used in the company base-case.

In addition, the EAG notes that the values are based on the EQ-5D-5L and the NICE reference case stipulates a preference for EQ-5D-3L values.[34] Summary score EQ-5D-5L values can be mapped to EQ-5D-3L using the published calculator from Hernandez Alava *et al*. 2020,[43] which was explored by the EAG. The average age of patients reported in Chapter 8 of the Kamudoni *et al*. 2014 thesis was 38.8 for USA patients and 42.8 for UK patients. Therefore, the age bracket of 35–45 was used in the mapping calculator. The mapped EQ-5D-3L resulted in much lower utility values than the 5L; HDSS 2 = 0.74, HDSS 3 = 0.70 and HDSS 4 = 0.57. As previously mentioned, it is unclear if the 5L utility values from Kamudoni *et al.* are based on a USA or UK value set. Therefore, these uncertainties remain in the mapped values to EQ-5D-3L. Furthermore, the EAG considers the mapped EQ-5D-3L values to be relatively low for the condition of interest and potentially lack's clinical validity. For example, the estimated value for HDSS = 4 of 0.57 is lower than the utility value applied and accepted by the NICE committee in a recent technology appraisal for progression-free survival patients with relapsed or refractory multiple myeloma after receiving four or more treatments (0.589).[44]

The EAG does not consider either the EQ-5D-5L values or the 5L values mapped to 3L to be appropriate for the EAG base-case analysis. Furthermore, the EAG is not aware of any alternative EQ-5D-3L values related to HDSS score in the existing literature. The EAG maintains that mapping available DLQI data from Hyp1-18/2016 Phase 3b to EQ-5D-3L should have been undertaken by the company as their reasons not to do so are not sufficiently justified. Such an analysis would have aligned with the NICE reference case, by providing more relevant and current values from the patient population of interest and using the NICE preferred EQ-5D-3L values. Additionally, this utility mapping analysis would have significantly contributed to the research base and reduced uncertainty surrounding the most appropriate values for the economic model. Consequently, due to the absence of appropriate utility values, the EAG is unable to propose a preferred base-case analysis. Instead, scenario options are provided utilising the EQ-5D values (both 5L and 5L mapped to 3L) based on Kamudoni *et al.* (see Section 5.2.3 for further details).

The EAG notes the disutility value for non-axillary sweating/hyperhidrosis is derived using assumptions based on the average utility values for HDSS health states used in the company's base-case. As described earlier, the EAG considers the health state utility values to be highly uncertain. The EAG considers the resulting disutility for non-axillary sweating/hyperhidrosis to be particularly high. Generally, the EAG considers the other reported disutility values to be appropriate when applied to severe AEs. However, none of the studies used to obtain adverse events, including the key trial, [redacted], with inconsistent definitions used across studies. As such, the EAG does not consider it appropriate to include adverse events in the EAG base case. See Section 4.2.5 for further details on this issue, and Section 5.2.2 for the EAG scenario and Section 5.2.3 for results using the EAG's preferred assumptions.

4.2.7 Resource use and costs

In the economic model, the company included costs relevant to drug acquisition, administration and patient monitoring, adverse events and subsequent treatment. Drug costs were sourced from the British National Formulary (BNF) or the NHS Drug Tariff.[45] Drug administration and monitoring costs were sourced from NHS 2023/24 National Cost Collection data dashboard and the Unit Costs of Health and Social Care 2023.[46]

A confidential price is available for botulinum toxin A and so the EAG has produced a confidential appendix to this report. Please refer to Section 5.4 for further details on analyses included in the confidential appendix.

4.2.7.1 Drug acquisition costs

The list price of GPB 1% cream is [redacted] per 50g tube. The treatment regimen for GPB 1% cream is two pump actuations per axilla, which is equivalent to 0.54g (1.08g in total for both axillae), applied once daily for four weeks, and then a minimum application of twice per week from week five onwards. The Summary of Product Characteristics (SmPC) for GPB 1% cream recommends continuous usage to maintain the treatment effect.[10] The cost per administration based on unit price and recommended dose is [redacted].

The company includes data on compliance with GPB 1% cream to adjust the cost per administration in the model. A compliance rate of [redacted]% is estimated based on the difference between the mean grams used in the first 29 days of treatment ([redacted]) from Hyp1-18/2016 Phase 3b and the

expected total dose for the first 29 days of treatment (1.08 g x 29 = 31.3 g). Based on the compliance rate, the company estimated the adjusted cost per administration of GPB 1% cream is [redacted].

Data on the mean number of applications per week of GPB 1% cream, up to week 72, were available for the safety analysis set of Hyp1-18/2016 Phase 3b and are presented in Table 24 of the CS. The company estimated the cost per cycle of GPB 1% cream by multiplying the compliance-adjusted cost per administration of GPB 1% cream by the mean number of applications for the relevant model cycle. After week 72, the company assumed that the mean number of applications at 72 weeks applied for the remainder of the model time horizon.

As mentioned previously, the company has used a basket approach for oral antimuscarinics. Table 49 presents the cost of each oral antimuscarinic and the assumed usage proportion in the basket. The company stated that the distribution of oral antimuscarinic usage is based on data obtained from the study by Wade *et al*. 2017.[11] It should be noted that the company assumed the proportion taking oral GPB is the same as the proportion taking oral glycopyrrolate from Wade *et al*.[11] The company has assumed that RDI for the comparators is 100%. Table 49 also provides the cost included for botulinum toxin A. The company has assumed that patients would be given two botulinum toxin A treatments per year.

The EAG notes that the company has used a concessionary price for propantheline bromide instead of the drug tariff price (£20.74), based on price data from January 2025 from Community Pharmacy England.[47] The company's justification for using a concessionary price is that since February 2024, the price of propantheline bromide has been over £100 due to supply issues. The EAG notes that minor fluctuations in the concessionary price of propantheline bromide were observed in the data from Community Pharmacy England between February 2024 and July 2025 and that the average price over that period was £103.41. As such, the company's choice to use the January 2025 price of £103.52 is not dissimilar to the average price.

Table 49. Comparator treatment costs

Treatment	Usage proportion	Dose	Pack size	Cost per pack	Cost per dose
Propantheline bromide	35.4%	15 mg, 3 times per day and 30 mg before bed (75 mg in total)	112 tablets (15 mg/ tablet)	£103.52	£4.62
Oxybutynin	46.2%	2.5 mg, 3 times per day (7.5 mg in total)	84 tablets (2.5 mg/ tablet)	£1.40	£0.05

Treatment	Usage proportion	Dose	Pack size	Cost per pack	Cost per dose
Oral GPB	18.5%	2 mg once a day	30 tablets (2 mg per tablet)	£198.00	£6.60
Weighted cost of oral antimuscarinics	**100%**	**-**	**-**	**-**	**£2.88**
Botulinum toxin A	100%	100U, every 6 months	1 x 100U vial	£129.90	£129.90
	0%*	150U, every 6 months	1 x 200U vial	£259.80	£259.80

Abbreviations: GPB, glycopyrronium bromide; U, unit

* Only explored in scenario analysis.

The total drug acquisition cost for GPB 1% cream, oral antimuscarinics and botulinum toxin A is [redacted], £387 and £400, respectively.

4.2.7.2 EAG critique

The EAG investigated the CSR for the Hyp1-18/2016 Phase 3a/3b trial and found that in Phase 3a, compliance with GPB 1% cream up to week 4 was estimated to be [redacted]%, which is approximately [redacted] than in Phase 3b for the same time point.[17] However, as the outcome data in the model for GPB 1% cream are derived from Hyp1-18/2016 Phase 3b, it is appropriate that compliance is also based on the same dataset. The EAG notes that in the CSR, the compliance rate for the different timepoints in Hyp1-18/2016 Phase 3b were available and are presented in Table 50. It is noted in the CSR that compliance after week 4 is based on being compliant with a minimum of two applications per week, as per the flexible dosing regimen.

Based on the data presented in Table 50, the EAG notes that compliance with GPB 1% cream [redacted]. The EAG considers that the average compliance over time is approximately [redacted], may be a conservative cost assumption.

Table 50. Compliance rate for GPB 1% cream from Hyp1-18/2016 Phase 3b (Table 5.4.3b of the CSR)[17]

Timepoint	Compliance rate
Company base – baseline to week 4	[redacted]
Week 4 - 8	[redacted]
Week 8 – 12	[redacted]
Week 12 – 28	[redacted]

Week 28 – 52	[redacted]
Week 52 – 72	[redacted]

Abbreviations: CSR, clinical study report; GPB, glycopyrronium bromide.

As discussed in Section 4.2.2.1, the EAG prefers the cost-effectiveness results to be separated by care setting and has included in its preferred assumptions separate results for primary care and secondary care. For the primary care model, the EAG's clinical experts considered that the main comparator would be propantheline bromide and for the secondary care model, the comparators would be modified-release oxybutynin 5mg once daily and botulinum toxin A. The cost of modified-release oxybutynin 5mg is £28.16 per pack of 28 tablets and this has been included in the EAG's preferred assumptions (Section 5.2.3).

The EAG considers that it is inappropriate to use a concessionary price for propantheline bromide in the model. The NICE manual states that "*for medicines that are mainly prescribed in primary care, base prices on the drugs tariff*".[34] The drug tariff price for propantheline bromide is £20.74.[48] The EAG notes that based on open prescribing data, from 2010 to Feb 2024, the price has been stable at £20.74 or just below.[49] As such, the EAG considers that the drug tariff price is the typical price for propantheline bromide and that a short-term concessionary price should not be used to inform decision making. The EAG has included the drug tariff price for propantheline bromide as part of its preferred assumptions, presented in Section 5.2.3.

As a secondary issue, the EAG notes that the BNF price for oxybutynin 2.5 mg used in the company's base case has been updated to £1.50 per pack of 84 tablets. Additionally, a cheaper price of £71.35 for oral GPB was available from Drugs and pharmaceutical electronic market information tool (eMIT). Both prices have been included as part of the model corrections, presented in Section 5.2.1.

4.2.7.3 Drug administration and monitoring costs

The company applied administration and monitoring costs for all treatments, based on an assumed healthcare setting (i.e. primary care and secondary care). For all treatments, the company assumed that patients are monitored on a quarterly basis in the first year, followed by annual monitoring thereafter.

The company stated that all administration and monitoring for patients receiving GPB 1% cream will be undertaken in primary care and therefore apply a cost of a general practitioner (GP) visit, sourced from PSSRU 2024.[50]

Based on feedback from clinical experts, the company stated that GPs are encouraged to use the advice and guidance (A&G) scheme to access advice from hospital specialists and that the management of severe PAHH is an area where this would be used to encourage management in primary care rather than referrals to secondary care. The company noted that the use of A&G services would be most applicable to treatment with antimuscarinics due to associated side effects.

The administration cost A&G service use consists of a GP visit plus a £20 cost of A&G services. For oral antimuscarinics, the company model assumes that 25% are administered through A&G services, 25% through primary care only and the remaining 50% via secondary care. Secondary care administration was costed using NHS Reference Costs 2023/24 dermatology outpatient appointment costs (£168).[51] The company assumed that monitoring costs will be applied in the same healthcare setting as the initial administration throughout the lifetime of the model, and therefore applies the same costs. For example, antimuscarinics monitoring costs are based on 25% primary care, 25% primary care plus A&G scheme and 50% secondary care.

In the company's model, all botulinum toxin A administration is undertaken in secondary care and is given every six months. The company applied administration costs related to botulinum toxin A administration based on assumptions made in Wade *et al*.,[11] which assumed 45 minutes of nurse time (£35.25) plus the NHS reference cost for intermediate skin procedures, general surgery (£156).[51] During clarification, the EAG requested further justification for the use of both a nurse administration costs and the NHS reference cost, beyond its use in Wade *et al.* and further information on what the NHS reference cost is intended to include. The company stated that in Wade *et al.* clinical experts had advised the approach of using both costs and therefore it was deemed appropriate for the current appraisal. The company was unable to state what was included in the NHS reference cost code. Instead, an alternative scenario analysis was provided, which used the weighted average cost of day case appointments for a range of skin disorders, with and without interventions (HRG code HD07). This resulted in a cost of £535; the company noted that this suggests that the cost used in the company base case, which combines the NHS reference cost of £156 plus 45 minutes nurse time, can be considered conservative.

In addition to the administration costs for botulinum toxin A, the company also applied a separate monitoring cost equivalent to that used for secondary care outpatient appointments for patients receiving antimuscarinics (£168), applied quarterly in the first year and annually thereafter.

A summary of the administration and monitoring costs used in the company model for each treatment can be found in Table 39 of the company submission.

4.2.7.4 EAG critique

The EAG's clinical experts highlighted that use of A&G services would only happen once to support diagnosis and treatment of a patient and that ongoing support would not be provided. Additionally, they advised that very few hyperhidrosis patients are seen through A&G services. In the Enhanced Service Specification document for A&G services published by NHS England it states, "*Practices will be entitled to claim a £20 Item of Service (IoS) fee per request for prereferral advice and guidance. Only one claim can be made per episode of care (i.e. multiple contacts between the practice and specialist for the same clinical issue are counted as one A&G referral)".*[52] Therefore, the EAG does not consider applying A&G costs beyond the initial appointment to be appropriate (**Key issue 9**, Section 1). During the clarification stage, the EAG requested, and the company supplied, a scenario in which the additional cost of A&G services is only applied to the first appointment for 10% of primary care patients in the antimuscarinics arm (see Section 5.1.1.2 for results). The EAG considers this scenario to be more appropriate for the primary care model that form the basis of the EAG preferred assumptions (see Section 5.2.3).

Additionally, the EAG's clinical expert advised that patients would not be seen quarterly after first administration for any treatments and would instead expect patients receiving both oral antimuscarinics and GPB 1% cream to be monitored annually in primary care, regardless of whether treatment was initially prescribed in secondary care (**Key issue 9**, Section 1). Furthermore, the EAG's clinical expert explained that botulinum toxin A patients would be monitored as part of their next scheduled treatment appointment (**Key issue 10**, Section 1). The EAG considers it more reflective of clinical practice to apply monitoring costs for antimuscarinics and GPB 1% cream annually only, based on the cost of a primary care visit and for botulinum toxin A monitoring costs to be excluded. This is included as part of the EAG's preferred assumptions (see Section 5.2.3).

The EAG was concerned that the administration and monitoring costs for botulinum toxin A were overestimated. The EAG's clinical expert stated that the time taken to review a patient and deliver treatment with botulinum toxin A would be around 20 minutes and conducted by a nurse (**Key issue 10**, Section 1). Therefore, the EAG requested the company to provide a scenario analysis in which the cost of botulinum toxin A administration was based on 20 minutes of nurse time. In response, the company stated that this was not in line with the experts in Wade *et al.* or published NHS

protocols and fails to capture the broader resource use involved. The EAG notes that only one of the protocols cited by the company was related to botulinum toxin A administration for PAHH.[53] The remaining were related to botulinum toxin A for anal fissure and cerebral palsy or other neurological conditions for children, all of which required general anaesthetic. As such, the EAG does not consider these to be relevant for PAHH as they would all require further resources and post-procedure observation. On the contrary, the protocol for botulinum toxin A for the treatment of PAHH specifically states that the appointment will last around 45 minutes with botulinum toxin A administration under each arm taking around 15 to 20 minutes. It also states that patients can go home straight after treatment and therefore no post-procedure observation is required. Two other patient information sheets for botulinum toxin A for hyperhidrosis from other NHS trusts suggest a treatment time of 20 minutes to one hour.[54, 55]

Based on the above, the EAG considers only the cost of nurse time for a 45-minute appointment to be most appropriate and is included as part of the EAG's preferred assumptions (see Section 5.2.3). However, based on the aforementioned protocol specific for PAHH, in the EAG preferred assumptions, the first administration of botulinum toxin A is given by a consultant and therefore uses the cost equivalent to "Outpatient care, Dermatology Service, WF01A, Non-admitted face-to-face attendance, consultant-led, first attendance". During the development of the EAG's report, the latest NHS Reference Costs was unavailable due to a website update. Therefore, the EAG used the cost available from 2022/23 (£177.01) and inflated this using the latest NHS Cost Inflation Index (NHSCII).[50] This resulted in a cost of £184.64 to be applied for the first BTX administration.

4.2.7.5 Treatment discontinuation

Table 51 summarises the treatment discontinuation data included in the company's model. The company applied the estimated 2-weekly discontinuation probability of each treatment for the entire duration of the model. The company explored scenario analyses around the discontinuation data used for each treatment and these are presented in Section 5.1.1.2.

Table 51. Summary of treatment discontinuation data included in the model

Treatment	Overall discontinuation rate	2-weekly discontinuation probability	Source & assumptions
GPB 1% cream	[redacted]	[redacted]	[redacted]
Oral antimuscarinics	50.9 %	5.3%	Wolosker *et al.* 2014.[56] RCT of oxybutynin in 431 patients with axillary hyperhidrosis. By 6 months, 188 patients had discontinued treatment. Reasons for discontinuation included: lack of improvement (n = 114), loss to follow-up (n = 34), opted for surgery (n = 26), AEs (n = 14).
Botulinum Toxin A	31.5 %	2.9%	Lowe *et al*. 2007.[22] Of the 214 patients that had one administration of botulinum toxin A, 91 completed the study (not eligible for retreatment due to maintained response) and 22 discontinued treatment. The company estimated the overall discontinuation rate based on the number of patients that discontinued plus 50% of the patients that completed the study after the first treatment.

Abbreviations: AE, adverse event; GPB, glycopyrronium bromide.

4.2.7.6 EAG critique

The EAG considers that assumptions made around the treatment discontinuation rate for oral antimuscarinics and botulinum toxin A are a primary driver of cost-effectiveness in the model (**Key issues 11 and 12**, Section 1). The results of the ITC demonstrated that both oral antimuscarinics and botulinum toxin A are [redacted] (Section 4.2.3.2). However, the company's base case results demonstrate that patients treated with GPB 1% cream are likely to experience a quality-adjusted life-year (QALY) gain of [redacted] and [redacted] compared to being treated with oral antimuscarinics and botulinum toxin A, respectively. The EAG found that the company base case results are driven by how quickly patients discontinue use of comparator treatments and move on to subsequent treatment, where patients experience no benefits of treatment (return to baseline HDSS scores) but incur costs.

The EAG considers that it is [redacted]

[redacted]. The issue of subsequent treatment benefit is discussed further in Section 4.2.8. However, the EAG notes several issues with the assumptions around the comparator discontinuation rates included in the model.

The EAG's clinical expert considered that most treatment discontinuations for oral antimuscarinics occur in the first month of treatment, with around 1/3rd of patients stop taking treatment. After the first month, the remaining patients are assumed to have a good response and tolerance to treatment and that the overall discontinuation rate going forward is around 10%. Additionally, the EAG's clinical expert advised that within two years, most patients are expected to have identified an effective treatment and are likely to remain on it long-term. As mentioned previously, the EAG considers that a shorter time horizon for the model may be more appropriate (Section 4.2.2.1).

Assuming a time horizon of two years based on the EAG's clinical expert view, the EAG calculated that the 2-week instantaneous rate of discontinuation is 0.20% for oral antimuscarinics after week 4. As such, the overall discontinuation rate, based on the EAG's clinical expert view is 43%, which is less than that used for the company's base case (50.9% overall, 5.3% per 2-week cycle), but the implementation of having a higher discontinuation rate early in the model, with a slower rate for the remainder of the model has a substantial impact on the cost-effectiveness results.

Upon EAG request, the company supplied a scenario implementing the EAG's clinical expert view on the discontinuation rate for oral antimuscarinics, which resulted in an estimated [redacted] and switched the incremental cost-effectiveness ratio (ICER) from dominant to [redacted]. When combined with a two-year time horizon, the [redacted], resulting in an ICER of [redacted]. The EAG acknowledges that parameter estimates informed by clinical experts are subject to uncertainty, but highlights that these QALY estimates are more in keeping with the ITC results for oral antimuscarinics.

With regards to botulinum toxin A, the EAG's clinical expert considered that a two-weekly discontinuation rate for botulinum toxin A is not reflective of current practice. They considered that after the first treatment, patients would be booked in for their second treatment and then response to treatment assessed at that appointment (after 6 months). At the second injection appointment, the dose would be adjusted based on response. As such, discontinuation of treatment is only likely

to happen at the third treatment, if patients aren't responding to botulinum toxin A. The EAG's clinical expert advice aligns with the data from Lowe *et al.* presented in Table 31 of the CS.

The EAG considers data on study completion from Lowe *et al*. 2007, should not inform treatment discontinuation (as has been included in the company base case) as the trial design was such that based on monitoring during the trial, patients were only eligible for retreatment with botulinum toxin A if they had a HDSS score of 3 or 4 and at least 50 mg of spontaneous resting axillary sweat over 5 minutes in each axilla.[22] Therefore, the EAG understands that patients who completed the study were those who were not eligible for retreatment due to maintained response to previous treatment.

Additionally, the Lowe *et al*. study is from 2007 and may not reflect the current clinical practice. The EAG's clinical expert advised that if patients have a good response to botulinum toxin A, most receive their next scheduled injections and can remain on treatment for many years. Therefore, the EAG considers it is more appropriate to apply botulinum toxin A treatment discontinuation in the model at the timepoint of each administration (every 6 months), using the discontinued data from Lowe *et al*. presented in Table 31 of the CS. Upon request from the EAG, the company supplied a scenario based on the EAG's preferred approach and while the ICER remained dominant, the estimated QALY gain [redacted] to [redacted].

The EAG considers that both discontinuation scenarios for the comparators are key drivers of cost-effectiveness and has therefore included them as part of its preferred assumptions, presented in Section 5.2.3.

4.2.7.7 Adverse event unit costs

The company assumed that the cost of treating all AEs, except for injection site pain, injection site bleeding, and non-axillary hyperhidrosis, would equate to the cost of a GP appointment and 10 minutes of a community-based pharmacist's time. Unit costs for a GP appointment (£45) and one hour of band-6 community pharmacist time (£57) were sourced from PSSRU, resulting in a total cost of £54.50 used in the model.[50]

The company assumed the cost to treat injection site pain and bleeding would be based on 10 minutes of a hospital-based pharmacist's time. One hour of band-6 hospital-based pharmacist time (£55) was sourced from PSSRU, resulting in a total cost of £9.17 used in the model.[50]

For non-axillary hyperhidrosis, the company assumed the cost would be equal to the total lifetime drug acquisition and administration costs of oral antimuscarinics delivered in secondary care (£792.80).

The weighted cost per cycle of AEs for GPB 1% cream, oral antimuscarinics and botulinum toxin A is [redacted], £15.14 and £1.80, respectively.

See Section 4.2.5 for the AE inclusion criteria in the economic model, AE incidence and duration for the intervention and comparators.

4.2.7.8 EAG critique

As discussed in Section 4.2.5.1, the EAG considers that the inclusion of the impacts of AEs is not appropriate given that the data included in the model are for mild and moderate events, which it considers is unlikely to have significant cost and quality of life implications. Nevertheless, there are two issues the EAG has with the company's estimation of the cost of AEs:

- The cost of an adverse event represents the cost to treat the event. However, in addition to the cost of a GP appointment, the company has included 10 minutes of pharmacist time, which is likely to represent dispensing of medicine, rather than a patient being treated by the pharmacist. As such, the EAG considers that the cost of pharmacist time should be excluded from the cost-effectiveness analysis.
- The cost of non-axillary hyperhidrosis is based on the company's modelling of oral antimuscarinics in the model. In the model, [redacted] non-axillary hyperhidrosis associated with botulinum toxin A treatment, as such, the EAG considers that the costs of treatment for this AE might be inflated.

The EAG's preferences is for the AEs to be excluded from the model entirely and has included this as part of its preferred assumptions, presented in Section 5.2.3.

4.2.8 Subsequent treatment

In the company's economic model, only the costs of subsequent treatment were included and not the benefits. Instead, the company assumed that patients returned their baseline HDSS score and accrued the utility values associated with that health state.

Upon entry to the subsequent treatment health state, patients incur a one-off cost of a basket of subsequent treatments. The distribution of subsequent treatments is dependent on the initial treatment received in the model. All subsequent treatments included in the model are assumed to be delivered in secondary care. Table 52 presents the distribution of subsequent treatments included in the model. The company assumed that patients in the oral antimuscarinics arm of the model try a different type of oral antimuscarinic in secondary care.

The company presented no evidence for the use of GPB 2% cream for the treatment of PAHH and in their clarification response, they stated that because the treatment is unlicensed, it has not been subjected to clinical studies. Nonetheless, GPB 2% cream has been included in the basket of subsequent treatments and the EAG's clinical expert did not disagree with its use as a third-line treatment option.

Table 52. Distribution of subsequent treatments included in the model

Subsequent treatments	GPB 1% cream	Oral antimuscarinics	Botulinum toxin
Antimuscarinics	10.0%	10.0%	50.0%
Botulinum toxin	90.0%	85.0%	0.0%
Unlicensed GPB 2% cream	0.0%	5.0%	50.0%

Abbreviations: GPB, glycopyrronium bromide

The cost of subsequent treatment is based on the mean drug acquisition, administration, monitoring and AE costs based on those estimated for initial treatment (Table 53). For GPB 2% cream, the company based its assumptions for administration, monitoring and adverse event costs on those estimated for GPB 1% cream.

To estimate the drug acquisition costs, the company assumed that the GPB 1% cream dose per administration for both axillae (1.08g) and compliance rate ([redacted]%) would be the same for GPB 2% cream. Based on a cost per 30 g tube of £129.70, sourced from the NHS Drugs Tariff,[45] the company estimated the cost per administration of GPB 2% cream was £3.53, which is [redacted] than the cost per administration of GPB 1% cream ([redacted]). The company applied the cost multiplier of [redacted] to the drug acquisition costs of GPB 1% cream to estimate the drug acquisition costs of GPB 2% cream (Table 53).

Table 53. Unit cost of individual subsequent treatments

Subsequent treatment	Drug acquisition	Administration and monitoring	Adverse Events	Total
Oral antimuscarinics	£402	£391	£277	£1,070

Subsequent treatment	Drug acquisition	Administration and monitoring	Adverse Events	Total
Botulinum toxin A	£413	£1,190	£63	£1,666
Unlicensed GPB 2% cream	[redacted]	£1,134	£47	[redacted]
Abbreviations: GPB, glycopyrronium bromide				

The weighted one-off cost of subsequent treatments, dependent on primary treatment, is presented in Table 54.

Table 54. Weighted cost of subsequent treatments, dependent on initial treatment, included in the model

Initial treatment	Weighted cost of subsequent treatment
GPB 1% cream	[redacted]
Oral antimuscarinics	[redacted]
Botulinum toxin	[redacted]
Abbreviations: GPB, glycopyrronium bromide	

4.2.8.1 EAG critique

The EAG considers that the company's approach to the modelling of subsequent treatments is fundamentally flawed, as patients incur subsequent treatment costs in the model, but return to their baseline HDSS score, resulting in costs and benefits that are not aligned (**Key issue 13**, Section 1). This is a particular problem as both oral antimuscarinics and botulinum toxin A were found to be [redacted] but are assumed by the company to have a higher discontinuation rate than GPB 1% cream. The EAG considers that the lack of benefit of subsequent treatment is a key driver of cost-effectiveness in the model.

The company referenced that their assumption around patients returning to baseline HDSS scores upon treatment discontinuation and initiation of subsequent treatment is aligned with that in Bloudek *et al*. 2021, but the EAG considers this to be incorrect. The paper states that, "*upon discontinuation with no subsequent treatment, patients reverted to baseline HDSS scores for the remainder of the modeled time horizon*".[29] Furthermore, in the Bloudek *et al*. response rates for subsequent therapies and associated benefits are included in the cost-effectiveness analysis. The company added a further justification for patients returning to baseline HDSS scores, stating that if they had failed second-line treatment, their underlying PAHH may be more difficult to treat and, as

such, they are unlikely to experience the same level of benefit as patients who are treated earlier but are still likely to incur the full costs of subsequent treatment. However, the company has presented no evidence to substantiate their claims around the effectiveness and HRQoL benefit of subsequent treatment.

The company's base case approach is biased against the comparators as the company's model estimates that most patients transition to subsequent treatment after [redacted] months for antimuscarinics and [redacted] years for botulinum toxin A and then spend approximately [redacted] years in the subsequent treatment health state only accruing the utility value associated with their baseline HDSS score. Patients on GPB 1% cream move to subsequent treatment after [redacted] years and spend approximately [redacted] years in the subsequent treatment health state.

As discussed in Section 4.2.2.1, the EAG considers that the model time horizon is potentially too long and may introduce unnecessary "noise" into the results, because the majority of the total costs and QALYs for each treatment arm is related to subsequent treatment. Additionally, the EAG considers that the company's approach to not include benefits of subsequent treatment is biased against the comparators, given the longer duration spent in the subsequent treatment health state.

The EAG raised its concerns with the company, which subsequently explored a scenario that estimated a treatment-specific weighted average utility for the subsequent treatment health state. The company first estimated the average HDSS 1 to 4 health state occupancy from the model for initial treatment (Table 55), then based on basket of subsequent treatment dependent on initial treatment (Table 52), estimated the average distribution of HDSS 1 to 4 scores for each treatment arm (Table 55) and applied the HDSS score utility values presented in Section 4.2.6.

Table 55. Mean distribution of HDSS scores for initial and subsequent treatment by model treatment arm

Initial treatment	Distribution across HDSS health states based on initial therapy				Distribution across HDSS health states based on subsequent therapy			
	1	2	3	4	1	2	3	4
GPB 1% cream	[redacted]							
Antimuscarinics	[redacted]							
Botulinum toxin	[redacted]							

Abbreviations: GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score.

As noted in Section 4.2.6.2, the EAG considers there are substantial uncertainties around the base case utility values in the model and alternative mapped utility values presented by the EAG are also

highly uncertain. As such, the EAG presents the average weighted utility of subsequent treatments estimated using both the company's base case values and the EAG's alternative values (Table 56).

Table 56. Average weighted utility values of subsequent treatments using the company base case values and the EAG's alternative values

Treatment arm	Company base case utility values – EQ-5D-5L	EAG alternative utility values – EQ-5D-3L
GPB 1% cream	0.801	0.713
Antimuscarinics	0.802	0.714
Botulinum toxin A	0.835	0.761

Abbreviations: EAG, External Assessment Group; GPB, glycopyrronium bromide.

The results of the company's scenario, using their base case utility values, have a substantial impact on the estimated QALY gain, [redacted] to [redacted] for the comparison with oral antimuscarinics and from [redacted] to [redacted] for the comparison with botulinum toxin A. When combined with a shorter time horizon of two years, there is a QALY [redacted] associated with GPB 1% cream against both comparators. When implementing the EAG's alternative utility values, the estimated incremental QALY for the comparison with oral antimuscarinics is [redacted] and [redacted] for the comparison with botulinum toxin A. With a time horizon of two years, there is a [redacted] associated with GPB 1% cream against both comparators.

The EAG prefers the company's scenario of using a weighted average utility for subsequent treatment over their base case assumption of patients reverting to baseline HDSS scores and as such has included it as part its preferred assumptions in Section 5.2.3. However, because of the underlying uncertainties around the HDSS score utility values (Section 4.2.6.2), the EAG does not present a preferred base case, but instead presents a range of ICERs using both the company's base case utility values and the EAG's alternative utility values for committee consideration.

The EAG's clinical expert validated the company's basket of subsequent treatments dependent on initial treatment (Table 52,and considered that the company's assumption of subsequent treatments did not reflect current clinical practice (**Key issue 14**, Section 1). Instead, they provided an alternative view of subsequent treatments in secondary care, outlined in Table 57. As described in Section 4.2.2.1, the EAG prefers the cost-effectiveness analysis to be separated and based on care setting, as such the estimates in Table 57 are based on patients receiving their initial treatment in primary care and secondary care. The EAG notes that for secondary care patients who have no NHS

further treatment, the EAG's clinical expert advised that approximately 1/3rd of these seek privately funded treatments.

The EAG ran a scenario in both the primary and secondary care models, exploring the EAG's clinical expert's view of the basket of subsequent treatment dependent on initial treatment with the EAG's preferred assumption of subsequent treatment benefit described earlier. In the secondary care model, for the 2/3rds of patients who have no further NHS treatment and do not seek privately funded treatment, the EAG considers it is reasonable for them to revert to their baseline HDSS scores. The distribution of HDSS scores and associated weighted utility values based on the EAG's clinical expert's view on the basket of subsequent treatment, dependent on initial treatment, is presented in Table 58 and results of the scenarios are presented in Section 5.1.1.2 for the secondary care model (company supplied the scenario) and Section 5.2.2 for the primary care model. The EAG has included its clinical expert's view on the subsequent treatment basket for the primary care and secondary care models as part of its preferred assumptions, presented in Section 5.2.3.

Table 57. EAG clinical expert's estimates of the subsequent treatment basket after initial treatment based on care setting

Subsequent treatment	Primary care model Proportion of subsequent therapies after initial:		Secondary care model Proportion of subsequent therapies after initial:		
	GPB 1% cream	Antimuscarinics	GPB 1% cream	Antimuscarinics	Botulinum toxin A
Antimuscarinics (secondary care)	20%	10%	10.0%	10.0%	25.0%
Botulinum toxin A (secondary care)	80%	90%	80.0%	63.0%	0.0%
Unlicensed GPB (secondary care)	-	-	0.0%	2.0%	25.0%
No further NHS treatment/ patients seek privately funded treatment	-	-	3.3%	8.3%	16.7%
No further NHS treatment/ patients discharged from care (secondary care model only)	-	-	6.7%	16.7%	33.3%

Abbreviations: GPB, glycopyrronium bromide

Table 58. Mean distribution of HDSS scores and weighted utility values based on EAG's clinical expert's view on the basket of subsequent treatment by model treatment arm

Initial treatment	Primary care model						Secondary care model					
	Distribution across HDSS health states based on subsequent therapy				Weighted utility value		Distribution across HDSS health states based on subsequent therapy				Weighted utility value	
	1	2	3	4	Company base case utility values	EAG alternative utility values	1	2	3	4	Company base case utility values	EAG alternative utility values
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	0.807	0.721	[redacted]	[redacted]	[redacted]	[redacted]	0.799	0.710
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	0.801	0.713	[redacted]	[redacted]	[redacted]	[redacted]	0.800	0.711
Botulinum toxin	-	-	-	-		-	[redacted]	[redacted]	[redacted]	[redacted]	0.803	0.714

Abbreviations: EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale.

5 Cost effectiveness results

Section 5.1 summarises the company's cost-effectiveness results, section 5.2 presents the External Assessment Group's (EAG's) additional work and preferred assumptions, and section 5.3 explores decision modifiers.

5.1 Company's cost effectiveness results

Table 59 and Table 60 presents the pairwise cost-effectiveness results of the company's updated (i.e., post factual accuracy check [FAC]) base case deterministic and probabilistic analyses versus antimuscarinics and botulinum toxin A, respectively.

The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Incremental results from the company's PSA are based on 1,000 simulations.

In the base-case probabilistic analysis of glycopyrronium bromide 1% cream (GPB 1% cream) versus antimuscarinics, GPB 1% cream was considered dominant based on lower incremental costs of [redacted] and an incremental quality-adjusted life-year (QALY) gain of [redacted]. The net health benefit (NHB) based on the probabilistic results is [redacted] and [redacted] at the £20,000 and £30,000 threshold, respectively. A positive NHB implies that overall population health would be increased because of the new intervention.

Table 59. Company's updated base case results (post FAC) versus antimuscarinics

Interventions	Total Costs (£)	Total LY*	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Antimuscarinics	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Probabilistic results							
Antimuscarinics	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: FAC, factual accuracy check; GPB, Glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

*Undiscounted

In the base-case probabilistic analysis of GPB 1% cream versus botulinum toxin A, GPB 1% cream was also considered dominant based on lower incremental costs of [redacted] and an incremental QALY gain of

[redacted]. The net health benefit (NHB) based on the probabilistic results is [redacted] and [redacted] at the £20,000 and £30,000 threshold, respectively.

Table 60. Company's updated base case results (post FAC) versus botulinum toxin A

Interventions	Total Costs (£)	Total LY*	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Probabilistic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: FAC, factual accuracy check; GPB, Glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

*Undiscounted

The company's base case fully incremental analysis results in antimuscarinics being dominated by GPB 1% cream and the results for botulinum toxin A are the same as in the pairwise comparison of GPB 1% cream versus botulinum toxin A, as shown in Table 60.

Figure 6 and Figure 7 shows PSA scatterplots of GPB 1% cream versus antimuscarinics and botulinum toxin A, respectively, with the corresponding cost-effectiveness acceptability curve (CEAC) is shown in Figure 8.

Figure 6. Scatterplot of PSA estimates on a cost-effectiveness plane of GPB 1% cream versus antimuscarinics

Figure 7. Scatterplot of PSA estimates on a cost-effectiveness plane of GPB 1% cream versus botulinum toxin

Figure 8. Cost-effectiveness acceptability curve

5.1.1 Company's sensitivity analyses

5.1.1.1 One-way sensitivity analysis

The company conducted one-way sensitivity analyses (OWSAs) to assess the impact on the incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) of varying specific parameters in isolation and to identify the main model drivers. The results are illustrated in the tornado diagrams presented Figure 9 and Figure 10 for GPB 1% cream versus antimuscarinics and botulinum toxin A, respectively. Due to dominant ICERs in the company's base-case analysis, it can be more difficult to intuitively interpret changes to the ICER. Therefore, the EAG has presented the tornado diagrams showing the impact on the NMB (£20,000 threshold). While the EAG notes that it may have been preferable to present the impact on the net health benefit (NHB), this was not available in the model for the EAG to easily conduct.

As shown in the figures below, varying utility values for health states HDSS 2–4 had the largest impact on the NMB. The EAG notes that the values used in the OWSA for utility values result in wide confidence intervals due to high variation around the mean. Therefore, the EAG considers that this may be the reason for the large impact on the results.

Figure 9. Tornado plot for antimuscarinics (reproduced from Figure 7 of the company's factual accuracy check response)

Figure 10. Tornado plot for botulinum toxin A (reproduced from Figure 9 of the company's factual accuracy check response)

5.1.1.2 Scenario analysis

The company undertook an extensive series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters, presented in Table 61. In addition, the company conducted several additional scenario analyses requested by the EAG, also presented in Table 61.

The EAG re-produced the scenarios using the company's automatic analysis in the company's updated model. It is noted that in the company's updated clarification response, the company used alternative time horizons for the scenarios against botulinum toxin A (20, 40 and 60 years) to those used for antimuscarinics (4, 5 and 10 years). In the table below, the EAG has presented the results for 4, 5 and 10 years for both comparators.

As shown in Table 61, GPB 1% cream remained the dominant treatment in all but two of the company's scenario analyses, in which the resulting ICER was less than £1,000.

As described in Section 4.2.2.1, the EAG prefers the cost-effectiveness results to be presented by care setting. Additionally, the EAG made corrections to the company model (Section 5.2.1). As such, the EAG's re-ran only the company's key EAG-requested clarification question (CQ) scenarios for the primary care setting (CQ scenario B1a) and the secondary care setting (CQ scenario B14) as the EAG considers they are the most important scenarios. Only one of the company's scenarios was included in the EAG's preferred assumptions (relative efficacy of GPB 1% cream vs. botulinum toxin A ≥1 HDSS score assumed the same as ≥2 HDSS score), and this is also included as part of the EAG's reanalysis of the company's key scenarios. Results of the EAG's reanalysis of key scenarios are presented in Appendix 7.4.

Table 61. Company updated scenario analysis, reproduced from the company's model, deterministic

Scenario description	Vs oral antimuscarinics			Vs botulinum toxin A		
	Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Company updated base-case	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Time horizon: 4-years	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Time horizon: 5-years	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Time horizon: 10-years	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Half cycle correction: excluded	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Discount rate: 0% costs and 0% outcomes	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Baseline characteristics: FASa	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Baseline characteristics: PPSb	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Baseline GPB 1% cream efficacy: PPSb	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Relative efficacy of GPB 1% cream vs. antimuscarinics based on PPSa	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Relative efficacy of GPB 1% cream vs. antimuscarinics based on Wade *et al.* 2017	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Relative efficacy of GPB 1% cream vs. botulinum toxin A based on PPSa	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Relative efficacy of GPB 1% cream vs. botulinum toxin A based on Wade *et al.* 2017	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Relative efficacy of GPB 1% cream vs. botulinum toxin A ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Dose of botulinum toxin A assumed 150U	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant

Scenario description	Vs oral antimuscarinics			Vs botulinum toxin A		
	Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Dose of botulinum toxin A assumed combined of 100U and 150U	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Relative efficacy for 2+ botulinum toxin A procedures based on Lowe et al. (2007)	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Relative efficacy for 2+ botulinum toxin A procedures based on a 10% reduction in OR	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Relative efficacy for 2+ botulinum toxin A procedures based on a 20% reduction in OR	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Maximum botulinum toxin A efficacy achieved at week 8	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Maximum botulinum toxin A efficacy achieved at week 12	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
1.8 botulinum procedures per year	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Cost of propantheline bromide of £20.74	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Dose per day of oxybutynin of 12.5mg	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Dose intensity for oral antimuscarinics assumed equal to GPB 1% cream	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Increase in discontinuation rate with GPB 1% cream of 10%	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Increase in discontinuation rate with GPB 1% cream of 20%	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Source of discontinuation for antimuscarinics from Millan-Cayetano *et al.* 2016	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Discontinuation for botulinum toxin A assumed as only those who were formally discontinued	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Discontinuation for botulinum toxin A assumed as those who were formally discontinued and no further treatment	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant

Scenario description	Vs oral antimuscarinics			Vs botulinum toxin A		
	Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
EAG requested scenarios						
B1a. 100% primary care model. GPB 1% cream versus antimuscarinics. Antimuscarinics consists of propantheline bromide only	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	N/A
B1b. 100% secondary care model. Comparators consist of oxybutynin 2.5mg (three times daily) and botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B2a. Time horizon: 72-weeks	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B2b, Time horizon: 2 years	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B3. Background mortality based on ONS life tables from 2017–2019	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B4. Peak efficacy for botulinum toxin A at 16 weeks	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B6. 20% Dysport for patients receiving two or more botulinum toxin A procedures	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B7. 0% non-axillary sweating adverse event for botulinum toxin A	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B11. 100% compliance with GPB 1% cream	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B12. Price of propantheline bromide set to £20.74	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B14. 100% secondary care model. Comparators consist of oxybutynin 5mg once daily and botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B15. 5% A&G administration for antimuscarinics in the first administration only	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B16. Non-half-cycle-adjusted monitoring appointments for botulinum toxin A	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant

Scenario description	Vs oral antimuscarinics			Vs botulinum toxin A		
	Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
B17. Cost of £535 for the administration of botulinum toxin	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B18. Primary care monitoring assumed for GPB 1% cream/antimuscarinics and no monitoring costs for botulinum toxin A	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B19a. Treatment duration for antimuscarinics informed by EAG clinical experts (33.3% discontinue treatment at week 4 (no discontinuations prior to that) and thereafter the 2-weekly rate of discontinuation of 0.20%).	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B19b. Treatment duration for antimuscarinics informed by EAG clinical experts and a 2-year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B20a. Treatment discontinuation for botulinum toxin A is applied according to the treatment schedule	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B20b. Treatment discontinuation for botulinum toxin A is applied according to the treatment schedule and assuming only formal discontinuations from Lowe *et al.* 2007	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B22a. Assuming the same HDSS response as observed for initial therapies for subsequent therapies	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]
B22b. Assuming the same HDSS response as observed for initial therapies for subsequent therapies and a 2-year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B22bi. Combination of scenarios B19b, B20b and B22b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Scenario description	Vs oral antimuscarinics			Vs botulinum toxin A		
	Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
B24a. Subsequent therapy distribution based on EAG's clinical feedback and assuming the same HDSS response as observed for initial therapies for subsequent therapies	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]
B24b. Scenario B24a plus two-year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: Δ, incremental; CQ, clarification question; GPB, Glycopyrronium bromide EAG, External Assessment Group; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; ONS, office of national statistics; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west

As discussed in Section 4.2.2.1, the EAG requested a scenario in which 100% of GPB 1% cream was administered in secondary care and compared against botulinum toxin A and oxybutynin (2.5mg three times daily). The EAG considers that this scenario should be presented as a full incremental analysis. This is also applicable to the requested scenario for CQ B14. Results can be seen in Table 62. In both scenarios, botulinum toxin A was dominated and GPB 1% cream versus antimuscarinics produced ICERs less than £10,000.

Table 62. Fully incremental results for EAG requested scenarios B1b and B14, deterministic only

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CQ B1b. 100% secondary care model. Comparators consist of oxybutynin 2.5mg (three times daily) and botulinum toxin A					
Antimuscarinics	[redacted]	[redacted]	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CQ B14. 100% secondary care model. Comparators consist of oxybutynin 5mg once daily and botulinum toxin A					
Antimuscarinics	[redacted]	[redacted]	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CQ, clarification question; GPB, Glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

5.2 EAG additional analyses

5.2.1 Model validation and face validity check

Section 3.12 in the company submission outlines the company's approach to the validation of the economic model. During the clarification stage, the EAG raised some concerns with the transparency in the model, which were rectified by the company. The EAG identified the following errors and updates needed in the economic model:

- Since the original company submission, the BNF price for oxybutynin has been updated to £1.50 and this has been updated in the model.
- A lower price of £71.35 for oral GPB was available from Drugs and pharmaceutical electronic market information tool (eMIT) and this has been updated in the model.
- In their clarification response, the company corrected hard-coded values for total costs of subsequent treatments in the model and instead derived the values from the model traces. However, the formula incorrectly references the wrong lookup value and so the model still relied on the hardcoded values. The EAG corrected the formula, located in the "Costs" tab, cells D62:D66 (changed from CQ_B22, to CQ_B21).
- In the economic model, the company reported the AE values for the 75U botulinum toxin A dose rather than the 50U dose from Lowe *et al*. 2007. The AE values should be 12% for injection site pain, 5% for injection site bleeding and 10% for non-axillary sweating. The EAG has corrected the data in the model.

The corrected company base results for oral antimuscarinics and botulinum toxin A are presented in Table 63 and Table 64, respectively.

Table 63. Corrected company's updated base case results (post FAC) versus antimuscarinics

Interventions	Total Costs (£)	Total LY*	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Interventions	Total Costs (£)	Total LY*	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							

Abbreviations: FAC, factual accuracy check; GPB, Glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

*Undiscounted

Table 64. Corrected company's updated base case results (post FAC) versus botulinum toxin A

Interventions	Total Costs (£)	Total LY*	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FAC, factual accuracy check; GPB, Glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

*Undiscounted

5.2.2 EAG's exploratory analyses using the company's base case

In Section 4 of this report, the EAG describes several scenarios that warrant further exploration in addition to the company's own sensitivity and scenario analyses to ascertain the impact of these changes on the incremental cost-effectiveness ratio (ICER).

As mentioned in Section 4.2.2.1, the EAG prefers the cost-effectiveness results to be presented by care setting. As such, the EAG's scenario results are presented separately for primary care and secondary care. The comparator in the primary care model is propantheline bromide and in the secondary care model, the comparators are modified-release oxybutynin and botulinum toxin A.

The scenarios that the EAG performed around the corrected company base case are summarised in Table 65. The EAG notes that as the modelling of subsequent treatments is intrinsically linked to the modelling of initial treatments, assumptions that affect botulinum toxin A in the secondary care model need to be applied in the primary care model. Results are presented in Table 66 and Table 67 for the primary care model and secondary care model, respectively.

Table 65. Summary of EAG's exploratory analyses using company's base case

Exploratory analysis number	Company's base case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
1	Inclusion of costs and disutilities associated with AEs	Exclusion of costs and disutilities associated with AEs	[redacted]	4.2.5.1
2	Administration and monitoring costs for antimuscarinics: 25% primary care; 25% primary care + A&G services	Primary care model (comparator is propantheline bromide). Administration costs for propantheline bromide: 90% primary care, 10% primary care + A&G services (1st appointment only)	Company states GPB 1% cream will be used in both primary and secondary care. As such, analysis reflects the primary care setting. Propantheline bromide is the only antimuscarinic with marketing authorisation for PAHH and GPs are less likely to use A&G services. Therefore, cost of A&G services is applied to a smaller proportion and is a one-off appointment and not ongoing support.	4.2.2.1 4.2.7.4
3	Quarterly monitoring of patients for the first year and reflects setting of administration.	Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care.	EAG's clinical expert advised that patients are not frequently monitored in clinical practice and that all appointments for GPB 1% cream and antimuscarinics would take place in primary care, irrespective of which setting they were initially prescribed.	4.2.7.4
4	Administration cost for botulinum toxin A based on NHS reference cost for intermediate skin procedures, general surgery and cost of 45-minutes of Band 6 nurse time. Cost of patient monitoring accounted for separately and assumed to be quarterly in the first year and annual thereafter.	1st administration of botulinum toxin A given by consultant and then cost of 45 minutes of Band 6 nurse time only for all subsequent administrations. Excludes additional monitoring costs for botulinum toxin A.	NHS protocols for botulinum toxin A treatment for PAHH advises that administration is given by a consultant for the 1st treatment and then by a nurse thereafter. Appointment time varies between 20 minutes to 1 hour. Monitoring of patients is assumed to talk place as part of the treatment administration appointment.	4.2.7.4

Exploratory analysis number	Company's base case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
5a	Basket of subsequent treatments dependent on primary treatment, but assumes all patients receive a next line treatment.	EAG's clinical expert advice on basket of subsequent treatment for the primary care model	Alternative, clinically plausible assumption based on clinical expert advice.	4.2.8.1
5b		EAG's clinical expert advice on basket of subsequent treatment for the primary care model + average weighted utility for the subsequent health state		
6	Basket of subsequent treatments dependent on primary treatment, but assumes all patients receive a next line treatment and revert to baseline HDSS scores.	EAG's clinical expert advice on basket of subsequent treatment for the secondary care model that also includes an assumption of no further treatment. This scenario also includes weighted average utility for the subsequent health state (CQ scenario B14 + B24)	Alternative, clinically plausible assumption based on clinical expert advice.	4.2.8.1
7	Lifetime horizon and basket of subsequent treatments dependent on primary treatment, but assumes all patients receive a next line treatment and revert to baseline HDSS scores.	Scenario 5b + two-year time horizon (primary care model only) Scenario 6 + two-year time horizon (secondary care model only)	Presents the impact of combined assumptions	4.2.2.1 4.2.8.1
8	Company's base case utility values are based on EQ-5D-5L and unclear if UK value set has been used	Mapped EQ-5D-3L utility values for the HDSS health states	NICE reference case does not recommend the use of utility values derived from the EQ-5D-5L.	4.2.6.2
9	Patients in the subsequent treatment health state revert to their baseline HDSS score and accrue utility values estimated from the EQ-5D-5L.	Mapped EQ-5D-3L utility values for the HDSS health states + weighted average utility value for the subsequent treatment health state.	Benefits of subsequent treatment should be included in the analysis and the weighted utility should be explored using the EQ-5D-3L utility values.	4.2.6.24.2.6.2 4.2.8.1
10	-	Scenario 5b + 8 (Primary care model only) Scenario 6 + 8 (secondary care model only)	Presents the impact of combined assumptions	4.2.8.1 4.2.6.2

Exploratory analysis number	Company's base case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
11	Patients in the subsequent treatment health state revert to their baseline HDSS score and accrue utility values estimated from the EQ-5D-5L, using lifetime horizon for the model.	Scenario 9 + 2-year time horizon	A shorter time horizon captures the most clinically important differences between treatments	4.2.2.1 4.2.6.2
12	-	Scenario 7 + 8	Presents the impact of combined assumptions	4.2.2.1 4.2.6.2 4.2.8.1

Abbreviations: AEs, adverse events; A&G, advice and guidance; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; OR, odds ratio; PAHH, primary axillary hyperhidrosis

Table 66. Results of EAG's deterministic exploratory analyses using company's base case – primary care model

Exploratory analysis number	Scenario applied to company's base case	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case	-	[redacted]	[redacted]	**Dominant**
Corrected company base case	-	[redacted]	[redacted]	**Dominant**
0	**Comparator is propantheline bromide (CQ B1a scenario)**	[redacted]	[redacted]	**Dominant**
1	Exclusion of costs and disutilities associated with AEs	[redacted]	[redacted]	Dominant
2	Administration costs for propantheline bromide: 90% primary care, 10% primary care + A&G services (1st appointment only)	[redacted]	[redacted]	Dominant
3	Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care.	[redacted]	[redacted]	Dominant
4	1st administration of botulinum toxin A given by consultant and then cost of 45 minutes of Band 6 nurse time only for all subsequent administrations. Excludes additional monitoring costs for botulinum toxin A.	[redacted]	[redacted]	Dominant
5a	EAG's clinical expert advice on basket of subsequent treatment for the primary care model	[redacted]	[redacted]	Dominant
5b	EAG's clinical expert advice on basket of subsequent treatment for the primary care model + weighted average utility value for the subsequent treatment health state	[redacted]	[redacted]	Dominant
7	Scenario 5b + two-year time horizon	[redacted]	[redacted]	[redacted]
8	Mapped EQ-5D-3L utility values for the HDSS health states	[redacted]	[redacted]	Dominant
9	Mapped EQ-5D-3L utility values for the HDSS health states + weighted average utility value for the subsequent treatment health state.	[redacted]	[redacted]	[redacted]
10	Scenario 5b + 8	[redacted]	[redacted]	Dominant
11	Scenario 9 and two-year time horizon	[redacted]	[redacted]	[redacted]
12	Scenario 5b + 11	[redacted]	[redacted]	[redacted]

Exploratory analysis number	Scenario applied to company's base case	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 67. Results of EAG's deterministic exploratory analyses using company's base case – secondary care model

Exploratory analysis number	Scenario applied to company's base case	Vs oral antimuscarinics			Vs botulinum toxin A		
		Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Company base case	**-**	[redacted]	[redacted]	**Dominant**	[redacted]	[redacted]	**Dominant**
Corrected company base case	**-**	[redacted]	[redacted]	**Dominant**	[redacted]	[redacted]	**Dominant**
0	**Comparators are modified-release oxybutynin 5 mg and botulinum toxin A (CQ scenario B14)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
1	Exclusion of costs and disutilities associated with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
3	Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
4	1st administration of botulinum toxin A given by consultant and then cost of 45 minutes of Band 6 nurse time only for all subsequent administrations. Excludes additional monitoring costs for botulinum toxin A.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
6	EAG's clinical expert advice on basket of subsequent treatment for the primary care model + weighted average utility value for the subsequent treatment health state (CQ scenario B24)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	Scenario 6 + two-year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
8	Mapped EQ-5D-3L utility values for the HDSS health states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
9	Mapped EQ-5D-3L utility values for the HDSS health states + weighted average utility value for the subsequent treatment health state.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	Scenario 6 + 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	Scenario 9 and two-year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Exploratory analysis number	Scenario applied to company's base case	Vs oral antimuscarinics			Vs botulinum toxin A		
		Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
12	Scenario 6 + 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: Δ, incremental; AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

5.2.3 EAG preferred assumptions

As discussed in Section 4.2.6.2, the EAG does not consider either the company's base case EQ-5D-5L utility values or the EAG's estimated EQ-5D-5L values mapped to EQ-5D-3L to be appropriate for an EAG base-case analysis. Furthermore, the EAG is not aware of any alternative EQ-5D-3L values related to HDSS score in the existing literature. Consequently, due to the absence of appropriate utility values, the EAG is unable to propose a preferred base-case analysis. Instead, the EAG presents two scenario options that uses the company base case utility values and the EAG's alternative utility values in addition to the EAG's other preferred assumptions, outlined in Table 68. As mentioned in Section 4.2.2.1, the company's proposed position in the treatment pathway for GPB 1% cream is in both primary and secondary care and as such the EAG has created two separate sets of preferred assumptions based on care setting (Table 68).

In summary, the EAG has provided the following scenarios in lieu of an EAG base case:

- Primary care model using the company's base case EQ-5D-5L utility values and the EAG's other preferred model assumptions.
- Secondary care model using the company's base case EQ-5D-5L utility values and the EAG's other preferred model assumptions.
- Primary care model using the EAG's alternative EQ-5D-3L mapped utility values and the EAG's other preferred model assumptions.
- Secondary care model using the EAG's alternative EQ-5D-3L mapped utility values and the EAG's other preferred model assumptions.

The EAG reiterates that mapping available DLQI data from Hyp1-18/2016 Phase 3b to EQ-5D-3L could have been undertaken by the company and the requested analysis would have aligned with the NICE reference case, by providing more relevant and current values from the patient population of interest and using the NICE preferred EQ-5D-3L value set. If the company provided the EQ-5D-3L values produced by this mapping exercise, it would resolve the current uncertainty regarding the utility values used in the model and facilitate the EAG in producing preferred base case results.

The EAG notes that as the modelling of subsequent treatments is intrinsically linked to the modelling of initial treatments, assumptions that affect botulinum toxin A in the secondary care model need to be applied in the primary care model.

Table 68. EAG's preferred assumptions by care setting

Primary care model	Section in report/ scenario reference	Secondary care model	Section in report/ scenario reference
Comparator is propantheline bromide	4.2.2.1 CQ scenario – B1a	Comparators are modified-release oxybutynin 5 mg and botulinum toxin A	4.2.2.1 CQ scenario B14
Price of propantheline bromide set to £20.74	4.2.7.2 CQ scenario – B12		
2-year time horizon	4.2.2.1 CQ scenario – B2b	2-year time horizon	4.2.2.1 CQ scenario – B2b
Treatment effectiveness of botulinum toxin A wanes after week 16	4.2.3.3 CQ scenario – B4	Treatment effectiveness of botulinum toxin A wanes after week 16	4.2.3.3 CQ scenario – B4
Botulinum toxin A OR for ≥1-point improvement in the HDSS score assumed to be the same as that for ≥2-point improvement	4.2.3.3 Company scenario	Botulinum toxin A OR for ≥1-point improvement in the HDSS score assumed to be the same as that for ≥2-point improvement	4.2.3.3 Company scenario
ONS lifetables from 2017-2019	4.2.4.1 CQ scenario – B3	ONS lifetables from 2017-2019	4.2.4.1 CQ scenario – B3
Removal of AEs	4.2.5.1 EAG scenario 1	Removal of AEs	4.2.5.1 EAG scenario 1
Administration costs for propantheline bromide: 90% primary care, 10% primary care + A&G services (1st appointment only)	4.2.7.4 EAG scenario 2	1st administration of botulinum toxin A given by consultant and then 45 minutes nurse time only for subsequent administrations. Excludes additional monitoring costs for botulinum toxin A.	4.2.7.4 EAG scenario 4
1st administration of botulinum toxin A given by consultant and then 45 minutes nurse time only for subsequent administrations. Excludes additional monitoring costs for botulinum toxin A.	4.2.7.4 EAG scenario 4		
Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care	4.2.7.4 EAG scenario 3	Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care	4.2.7.4 EAG scenario 3
EAG discontinuation rate for antimuscarinics	4.2.7.6 CQ scenario – B19a	EAG discontinuation rate for antimuscarinics	4.2.7.6 CQ scenario – B19a

Primary care model	Section in report/ scenario reference	Secondary care model	Section in report/ scenario reference
Botulinum toxin A discontinuation rate applied to each administration and only using Lowe *et* al. 2007 discontinuation data	4.2.7.6 CQ scenario – B20 (only formal discontinuations from Lowe et al. 2007).	Botulinum toxin A discontinuation rate applied to each administration and only using Lowe *et* al. 2007 discontinuation data	4.2.7.6 CQ scenario – B20 (only formal discontinuations from Lowe et al. 2007).
EAG clinical expert view on basket of subsequent treatment	4.2.8.1 EAG scenario 5	EAG clinical expert view on basket of subsequent treatment and average weighted utility value for subsequent treatment health state	4.2.8.1 *CQ scenario – B24
Average weighted utility value for subsequent treatment health state	4.2.8.1 CQ scenario – B22		

Abbreviations: AEs, adverse events; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; OR, odds ratio.

* The company's scenario for the EAG's clinical expert view on subsequent treatment includes the scenario for the weighted HDSS utility value to account for the QALYs associated with patients taking private treatment and those that have no further treatment and thus return to baseline HDSS score.

5.2.3.1 Primary care model – company base case utilities

Table 69 presents the cumulative results of the EAG's preferred assumptions using the company's base case utility values. Deterministic and probabilistic results of the scenario are presented in Table 70.

Table 69. Primary care model: cumulative deterministic results using the EAG's preferred model assumptions and the company's base case utility values – GPB 1% cream versus propantheline bromide

Preferred assumption	Exploratory analysis number	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Company base case	-	[redacted]	[redacted]	Dominant
Corrected company base case	-	[redacted]	[redacted]	Dominant
Comparator is propantheline bromide	CQ scenario – B1a	[redacted]	[redacted]	Dominant
Price of propantheline bromide set to £20.74	CQ scenario – B12	[redacted]	[redacted]	[redacted]
2-year time horizon	CQ scenario – B2b	[redacted]	[redacted]	Dominant
Treatment effectiveness of botulinum toxin A wanes after week 16	CQ scenario – B4	[redacted]	[redacted]	Dominant

Preferred assumption	Exploratory analysis number	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Botulinum toxin A OR for ≥1-point improvement in the HDSS score assumed to be the same as that for ≥2-point improvement	Company scenario	[redacted]	[redacted]	Dominant
ONS lifetables from 2017-2019	CQ scenario – B3	[redacted]	[redacted]	Dominant
Removal of AEs	EAG scenario 1	[redacted]	[redacted]	Dominant
Administration costs for propantheline bromide: 90% primary care, 10% primary care + A&G services (1st appointment only)	EAG scenario 2	[redacted]	[redacted]	Dominant
Apply consultant cost for first botulinum toxin A administration and nurse 45 minutes for subsequent	EAG scenario 4	[redacted]	[redacted]	Dominant
Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care	EAG scenario 3	[redacted]	[redacted]	Dominant
EAG discontinuation rate for antimuscarinics	CQ scenario – B19a	[redacted]	[redacted]	[redacted]
Botulinum toxin A discontinuation rate applied to each administration and only using Lowe *et al.* 2007 discontinuation data.	CQ scenario - B20 (only formal discontinuations from Lowe et al. 2007).	[redacted]	[redacted]	[redacted]
EAG expert view on basket of subsequent treatment	EAG scenario 5	[redacted]	[redacted]	[redacted]
Average weighted utility value for subsequent treatment health state	CQ scenario – B22	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 70. Primary care model - EAG scenario using preferred model assumptions and the company's base case utility values – GPB 1% cream versus propantheline bromide

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Propantheline bromide	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Probabilistic results							
Propantheline bromide	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

5.2.3.2 Primary care model – EAG alternative utility values

Table 71 presents the cumulative results of the EAG's preferred assumptions using the EAG's alternative utility values. Deterministic and probabilistic results of the scenario are presented in Table 72.

Table 71. Primary care model: cumulative deterministic results using the EAG's preferred model assumptions and the EAG's alternative utility values – GPB 1% cream versus propantheline bromide

Preferred assumption	Exploratory analysis number	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Company base case	-	[redacted]	[redacted]	Dominant
Corrected company base case	-	[redacted]	[redacted]	Dominant
Comparator is propantheline bromide	CQ scenario – B1a	[redacted]	[redacted]	Dominant
Price of propantheline bromide set to £20.74	CQ scenario – B12	[redacted]	[redacted]	[redacted]
2-year time horizon	CQ scenario – B2b	[redacted]	[redacted]	Dominant
Treatment effectiveness of botulinum toxin A wanes after week 16	CQ scenario – B4	[redacted]	[redacted]	Dominant
Botulinum toxin A OR for ≥1-point improvement in the HDSS score assumed to be the same as that for ≥2-point improvement	Company scenario	[redacted]	[redacted]	Dominant
ONS lifetables from 2017-2019	CQ scenario – B3	[redacted]	[redacted]	Dominant
Removal of AEs	EAG scenario 1	[redacted]	[redacted]	Dominant

Preferred assumption	Exploratory analysis number	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Administration costs for propantheline bromide: 90% primary care, 10% primary care + A&G services (1st appointment only)	EAG scenario 2	[redacted]	[redacted]	Dominant
Apply consultant cost for first botulinum toxin A administration and nurse 45 minutes for subsequent	EAG scenario 4	[redacted]	[redacted]	Dominant
Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care	EAG scenario 3	[redacted]	[redacted]	Dominant
EAG discontinuation rate for antimuscarinics	CQ scenario – B19a	[redacted]	[redacted]	[redacted]
Botulinum toxin A discontinuation rate applied to each administration and only using Lowe *et al*. 2007 discontinuation data.	CQ scenario - B20 (only formal discontinuations from Lowe et al. 2007).	[redacted]	[redacted]	[redacted]
EAG expert view on basket of subsequent treatment	EAG scenario 5	[redacted]	[redacted]	[redacted]
Average weighted utility value for subsequent treatment health state	CQ scenario – B22	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 72. Primary care model - EAG scenario using preferred model assumptions and the EAG's alternative utility values – GPB 1% cream versus propantheline bromide

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Propantheline bromide	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Propantheline bromide	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

5.2.3.3 Secondary care model - company base case utilities

Table 73 presents the cumulative results of the EAG's preferred assumptions using the company's base case utility values. Deterministic and probabilistic results of the scenario for modified-release oxybutynin and botulinum toxin A are presented in Table 74 and Table 75, respectively. Fully incremental results are presented in Table 76.

Table 73. Secondary care model: cumulative deterministic results using the EAG's preferred model assumptions and the company's base case utility values

Preferred assumption	Exploratory analysis number	Vs modified release oxybutynin			Vs botulinum toxin A		
		Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Company base case	-	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Corrected company base case	-	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Comparators are modified-release oxybutynin 5 mg and botulinum toxin A	CQ scenario – B14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
2-year time horizon	CQ scenario – B2b	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Treatment effectiveness of botulinum toxin A wanes after week 16	CQ scenario – B4	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Botulinum toxin A OR for ≥1-point improvement in the HDSS score assumed to be the same as that for ≥2-point improvement	Company scenario	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
ONS lifetables from 2017-2019	CQ scenario – B3	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Removal of AEs	EAG scenario 1	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Apply consultant cost for first botulinum toxin A administration and nurse 45 minutes for subsequent	EAG scenario 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Preferred assumption	Exploratory analysis number	Vs modified release oxybutynin			Vs botulinum toxin A		
		Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care	EAG scenario 3	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
EAG discontinuation rate for antimuscarinics	CQ scenario – B19a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Botulinum toxin A discontinuation rate applied to each administration and only using Lowe *et al*. 2007 discontinuation data.	CQ scenario - B20 (only formal discontinuations from Lowe et al. 2007).	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG expert view on basket of subsequent treatment and average weighted utility value for subsequent treatment health state	CQ scenario – B24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 74. Secondary care model - EAG scenario using preferred model assumptions and the company's base case utility values – GPB 1% cream versus modified-release oxybutynin

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Modified-release oxybutynin	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Modified-release oxybutynin	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 75. Secondary care model - EAG scenario using preferred model assumptions and the company's base case utility values – GPB 1% cream versus botulinum toxin A

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 76. Fully incremental analysis (based on PSA results) – secondary care model, company base case utility values

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
GPB 1% cream	[redacted]	[redacted]	[redacted]	-	-	-	-

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Modified-release oxybutynin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

5.2.3.4 Secondary care model – EAG alternative utility values

Table 77 presents the cumulative results of the EAG's preferred assumptions using the company's base case utility values. Deterministic and probabilistic results of the scenario for modified-release oxybutynin and botulinum toxin A are presented in Table 78 and Table 79, respectively. Fully incremental results are presented in Table 80.

Table 77. Secondary care model: cumulative deterministic results using the EAG's preferred model assumptions and the EAG's alternative utility values

Preferred assumption	Exploratory analysis number	Vs modified-release oxybutynin			Vs botulinum toxin A		
		Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Company base case	-	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Corrected company base case	-	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Comparators are modified-release oxybutynin 5 mg and botulinum toxin A	CQ scenario – B14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
2-year time horizon	CQ scenario – B2b	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Treatment effectiveness of botulinum toxin A wanes after week 16	CQ scenario – B4	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Botulinum toxin A OR for ≥1-point improvement in the HDSS score assumed to be the same as that for ≥2-point improvement	Company scenario	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
ONS lifetables from 2017-2019	CQ scenario – B3	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Removal of AEs	EAG scenario 1	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Apply consultant cost for first botulinum toxin A administration and nurse 45 minutes for subsequent	EAG scenario 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Preferred assumption	Exploratory analysis number	Vs modified-release oxybutynin			Vs botulinum toxin A		
		Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care	EAG scenario 3	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
EAG discontinuation rate for antimuscarinics	CQ scenario – B19a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Botulinum toxin A discontinuation rate applied to each administration and only using Lowe *et al*. 2007 discontinuation data.	CQ scenario - B20 (only formal discontinuations from Lowe et al. 2007).	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG expert view on basket of subsequent treatment and average weighted utility value for subsequent treatment health state	CQ scenario – B24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 78. Secondary care model - EAG scenario using preferred model assumptions and the EAG's alternative utility values – GPB 1% cream versus modified-release oxybutynin

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Modified-release oxybutynin	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Modified-release oxybutynin	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 79. Secondary care model - EAG scenario using preferred model assumptions and the EAG's alternative utility values – GPB 1% cream versus botulinum toxin A

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 80. Fully incremental analysis (based on PSA results) – secondary care model, EAG alternative utility values

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
GPB 1% cream	[redacted]	[redacted]	[redacted]	-	-	-	-

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Modified-release oxybutynin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

5.3 Decision Modifiers

5.3.1 QALY weighting for severity

The company has not made a case for a severity modifier to be applied to the base case QALY estimate and the EAG considers that to be appropriate.

5.3.2 Uncaptured benefits

Outlined in section 6.2.36 of the NICE health technology evaluations manual, committees can consider uncaptured benefits when making recommendations about a technology if:

- its decisions have a bearing on broader social considerations and the extent that these are covered by principles on social value judgements on the NICE website.
- there are strong reasons to suggest that the health benefits of the technology have been inadequately captured and may therefore misrepresent the health utility gained.
- a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services, or are associated with significant benefits other than health, only when requested specifically by the Department of Health and Social Care as part of the remit.

The company has considered there are several uncaptured benefits of GPB 1% cream that are not captured in the QALY calculation including:

- Convenience for patients as it is a topical medicine.
- Improved patient accessibility as it can be prescribed in primary care.
- A favourable safety profile compared to oral antimuscarinics.

The EAG considers that company's summary of uncaptured benefits does not meet the criteria outlined above. In particular, the company has included model parameters to capture the use of GPB 1% cream in primary care, as well as data on adverse events in their cost-effectiveness analysis and so these are captured in their base case QALY calculation. The EAG considers that the committee should rely on estimates of the ICER as the basis for decision making.

5.3.3 *Health inequalities*

The company has outlined two areas which they considered were potential equality issues, but for general hyperhidrosis and not specific to severe primary axillary hyperhidrosis (PAHH). The company's concerns are summarised below:

- The NICE final scope outlines adults as the population of interest based on the proposed marketing authorisation for GPB 1% cream. However, the company considers that hyperhidrosis commonly occurs in childhood and adolescence. Based on the proposed marketing authorisation for GPB 1% cream, which only includes adults, the EAG does not consider this to be an equality issue.
- Patients with hyperhidrosis often incur substantial out-of-pocket costs, primarily due to the ongoing need for absorbent clothing and hygiene. The EAG considers that the limited NHS budget is primarily focused on the care of patients rather than the indirect costs associated with a condition like hyperhidrosis.

5.4 Confidential comparator and subsequent treatment prices

The EAG has produced a confidential appendix to the EAG report which considers the confidential arrangements for botulinum toxin A. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses.

5.5 Conclusions of the cost effectiveness sections

The EAG considers the company's submission lacks an unbiased estimate of the ICER for GPB 1% cream. The company has proposed that GPB 1% cream would only be used in primary care and this assumption is included in the model. However, the company has also stated that they expect a small proportion of patients in secondary care will use GPB 1% cream and that this will displace both oral antimuscarinics and botulinum toxin A, but do not present separate cost-effectiveness results by care setting. Furthermore, the estimated QALYs in the company's base case, are derived from using EQ-5D-5L utilities (which isn't recommended by NICE). Given these two issues, the EAG considers that the company's ICERs are unsuitable for committee decision-making.

Another of the EAG's key concerns is that the company's indirect treatment comparison estimated that both oral antimuscarinics and botulinum toxin A are [redacted]. However, the company estimated

a [redacted] with GPB 1% cream. There are several uncertainties with the key assumptions in the company's model that the EAG considers are potentially biased against the comparators and thus influencing the [redacted] and also driving the company's estimated [redacted] and these are summarised below.

- The company assumed the treatment effect of botulinum toxin A treatment wanes four weeks after treatment until the next administration at 6 months. However, the EAG's clinical expert considered botulinum toxin A is one of the most effective treatments for severe PAHH and the treatment effect lasts for up to four months, after which the effect wanes.
- Upon treatment discontinuation, patients enter the subsequent treatment health state where they incur the cost of treatments but not the benefits. From the model, the EAG found that patients in all treatment arms spend most of the model time horizon in the subsequent health state ([redacted] years for GPB 1% cream, ~[redacted] years for the comparators). In the company's base case, the discontinuation rates for the comparators are higher than with GPB 1% cream and so most of the QALY differences are driven by treatment discontinuation and time spent in the subsequent treatment health state.
- The basket of oral antimuscarinics includes oral GPB, which is relatively expensive compared to propantheline bromide and oxybutynin. However, the EAG's clinical expert advised that in primary care, propantheline bromide is the main oral antimuscarinic prescribed by GPs as it is the only antimuscarinic to have marketing authorisation for PAHH and in secondary care, consultants prefer to use modified-release oxybutynin 5 mg, both of which result in cheaper costs than the company's basket approach.
- The company assumed costs for botulinum toxin A that the EAG considers are unlikely to be incurred in the NHS, including additional monitoring of patients outside of the twice-yearly treatment and an NHS reference cost which the company has been unable to appropriately justify including in the model.
- Adverse events for all treatments in the model are based on data for [redacted], which the EAG's clinical expert advised would be unlikely to incur additional costs outside of monitoring, dose reduction or treatment discontinuation, which (except for dose reduction) are captured in the model.

In addition to the above issues, because of the company's use of EQ-5D-5L utilities, the EAG mapped the values to the EQ-5D-3L but considers the values were not appropriate for an EAG base case as they potentially lack clinical validity, especially when compared other disease areas, such as multiple

myeloma.[44] As such, the EAG has been unable to produce a preferred base case, but instead presents scenarios for primary care and secondary care using its preferred assumptions and exploring the company's base case utility values and its alternative mapped EQ-5D-3L values.

The EAG maintains that mapping available DLQI data from Hyp1-18/2016 Phase 3b to EQ-5D-3L could have been undertaken by the company as their reasons not to do so are not sufficiently justified. Such an analysis would have aligned with the NICE reference case, by providing more relevant and current values from the patient population of interest, which is also the same population use to derive treatment effectiveness for GPB 1% cream and using the NICE preferred EQ-5D-3L values.

In conclusion, the EAG considers that given the key uncertainties and the substantial number alternative preferred assumptions explored, the company's base case is not reliable and presents a biased view of the cost-effectiveness of GPB 1% cream for treating severe PAHH.

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7 Appendices

7.1 Baseline characteristics for Hyp-18/2016 Phase3a FASa and Phase 3b FASnewb

Table 81. Patient demography and baseline characteristics for Hyp-18/2016 Phase3a FASa population (reproduced from Table 4 of the CS)

Demography	Characteristic	GPB 1% cream (N = 87)	Placebo (N = 84)	Total (N = 171)
Sex, N (%)[a]	Male	44 (50.6)	43 (51.2)	87 (50.9)
	Female	43 (49.4)	41 (48.8)	84 (49.1)
Race, N (%)[a]	White	86 (98.9)	81 (96.4)	167 (97.7)
	Black	1 (1.1)	-	1 (0.6)
	Asian	-	2 (2.4)	2 (1.2)
	Other	-	1 (1.2)	1 (0.6)
Baseline characteristics				
Age [years], median (range)		36.0 (18 to 65)	36.0 (18 to 65)	36.0 (18 to 65)
Body height [cm], median (range)		175.00 (155.0 to 198.0)	173.00 (153.0 to 196.0)	173.00 (153.0 to 198.0)
Body weight [kg], median (range)		76.40 (49.0 to 114.3)	76.10 (50.0 to 117.8)	76.40 (49.0 to 117.8)
sBMI [kg/m²], median (range)		25.50 (18.4 to 32.0)	25.05 (19.5 to 32.0)	25.10 (18.4 to 32.0)
BSA [m²], median (range)		1.94 (1.5 to 2.4)	1.90 (1.5 to 2.5)	1.93 (1.5 to 2.5)
Sweat production [mg], median (range)[b]		227.60 (0.2 to 1180.9)	252.25 (11.0 to 1012.8)	NA

N = 0 is shown as '-'

Source: Hyp-18/2016 Phase3a/b CSR[17]

a Percentages are based on the number of patients in the treatment group.

b At Baseline, values below 50 mg were allowed.

Abbreviations: BMI, body mass index; BSA, body surface area; FASa, full analysis set (Phase 3a); GPB, glycopyrronium bromide; N, number of patients; NA, not applicable.

Table 82. Patient demography and baseline characteristics for Hyp1-18/2016 Phase 3b FASb and FASnewb (reproduced from Table 5 of the CS)

Demography		FASb (N = 518)		FASnewb (N = 357)	
Sex, N (%)[a]	Male	244	(47.1)	160	(44.8)
	Female	274	(52.9)	197	(55.2)
Race, N (%)[a]	White	494	(95.4)	337	(94.4)
	Black	4	(0.8)	3	(0.8)
	Asian	8	(1.5)	6	(1.7)
	Other	12	(2.3)	11	(3.1)
Age [years], median (range)		33.0	(18 to 65)	32.0	(18 to 65)
BMI [kg/m²], median (range)		25.25	(18.1 to 32.3)	25.40	(18.1 to 32.3)
BSA [m²], median (range)		1.91	(1.28 to 2.60)	1.91	(1.28 to 2.60)
Sweat production [mg], median (range)[b]		NA		212.40	(0.2 to 1667.1)[c]

Source: Hyp-18/2016 Phase3a/b CSR[17]

Notes: [a] Percentages are based on the number of patients in each analysis set. [b] Assessed for newly recruited patients only. Missing baseline values were replaced with values from the GM assessments at Screening 2b. [c] The sweat production at Baseline was <50 mg in some patients; eligibility was assessed at Screening 2b.

Abbreviations: BMI, body mass index; BSA, body surface area; FAS(new)b, full analysis set ([patients newly recruited to] Phase 3b); GM, gravimetric measurement; N, number of patients; NA, not applicable.

7.2 EAG critique of the company's SLR methods

Table 83. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods

Data sources	Appendix B.1.1	**Appropriate**
		The following databases were searched:
		• Embase® (via Embase.com);
		• MEDLINE® (via Embase.com) and MEDLINE In-Process® (via PubMed.com);
		• The Cochrane Library (via wiley.com), including
		  ○ The Cochrane Database of Systematic Reviews (CDSR);
		  ○ The Cochrane Central Register of Controlled Trials (CENTRAL).
		
		The following conferences relevant to dermatology were also searched between 2023 and 2025:
		• World Congress of Dermatology;
		• IMCAS (Dermatology and Aesthetic & Plastic Surgery);
		• European Academy of Dermatology and Venereology (EADV);
		• British Association of Dermatologists (BAD).
		
		The following HTA bodies were reviewed for relevant records:
		• National Institute for Health and Care Excellence (NICE);
		• Canada's Drug Agency (CDA);
		• Pharmaceutical Benefits Advisory Scheme (PBAC).
		
		The following additional sources were searched for relevant data within the last 10 years:
		• NIHR Innovation Observatory;
		• NIHR UK Journals Library;
		• Agency for Healthcare Research and Quality;
		• International Clinical Trial Registry Platform;
		• European Union Clinical Trials Register.
		
		Additionally, a review of SLRs and NMAs identified within the searches was performed to identify relevant primary publications that had not already been identified.

Search strategies	Appendix B.1.2	**Some concerns about study filters and consistency of searches across databases** Searches were performed in March 2025, meaning they are very recent which should capture the most current evidence. However, some limitations of these searches are described under the headings below. ***Filtering for study design*** Searches were broad, aiming to capture studies regardless of study design. However, the way this has been done is unnecessarily complex and may have led to some relevant records being missed. For MEDLINE® and Embase® searches, filters for different types of study have been added to the search strategy and combined using the 'OR' function with the aim of identifying each of these different study types (Tables 1 and 2 in the company submission appendices). The EAG considers that this was unnecessary and instead the searches should have left out filters for study design completely; the company's strategy would have missed any records within databases that were either not indexed regarding study design or were incorrectly indexed and did not otherwise mention study design in the titles or abstracts, particularly a concern for more complex study types such as single-arm trials and real-world studies where filters are not as well validated and a wide range of terminology may be used to describe them. The EAG was unable to test the potential impact of this on the retrieval of records but considers it possible that some relevant studies may have been missed in the searches due to this approach. Furthermore, the EAG considers that the search filters used are unlikely to have been validated, given the one used for RCTs is substantially more complex than those typically used elsewhere, including the Cochrane RCT filter (Section 4.4.7 of the Cochrane Handbook for Systematic Reviews of Interventions).[57] It is unclear if a similar approach was performed for the search of MEDLINE In-Process® as the search strategy for this search has not been provided. This was not an issue for the CDSR and CENTRAL as no study design filters were used. ***Thoroughness and consistency of search terms*** Searches appropriately include a mixture of keywords and subject heading terms. However, the EAG is concerned that the thoroughness of some of the searches may be limited and there is clear inconsistency between searches in some cases. For example, the string to identify the hyperhidrosis population is broader in the Embase® search compared to the MEDLINE® search (Tables 2 and 1 of the company submission appendices, respectively); subject heading terms for "hyperhidrosis" have been used in both, but the search for keywords in the MEDLINE® search is likely to limit results, given specific terms of "axillary hyperhidrosis", "primary hyperhidrosis" and "severe hyperhidrosis" are included, with no inclusion of the broader "hyperhidrosis" term which has been included in the Embase® search.

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
		Search strings for other components such as interventions and comparators appear to be broad in both of these searches, although some terms have been included unnecessarily as the records captured would already have been captured by earlier terms (for example, "glycopyrronium" alone and "glycopyrronium" AND "bromide" as a combined term was included in the MEDLINE® search, the latter of which is unnecessary as the single term "glycopyrronium" would capture these). Furthermore, there are additional examples where the strings appear to be more thorough in the Embase® search compared to MEDLINE®, for example, the alternative keywords used for oxybutynin and benztropine are notable examples where a larger number of keywords have been included in the searches within Embase®. Similarly, the searches of the Cochrane Library appear to be less detailed compared to Embase®. Therefore, there is a concern that the MEDLINE® and Cochrane Library searches in particular were not as robust as they could have been. ***Overall concerns*** On review of some published SLRs in the same area,[11, 58-62] the EAG is reassured that it is unlikely that the concerns discussed above have led to any key RCTs (RCTs are the focus for comparator evidence and used within the ITCs performed in this submission) of the intervention and comparators of interest being missed. While not all RCTs included in these other reviews were picked up in this SLR, most were and those that were not identified are not studies that could be used as alternative or additional sources of evidence for interventions and comparators in this submission (i.e. they do not match the criteria for the intervention and/or comparators and/or are within different populations). Some non-randomised evidence has been utilised in the submission for GPB 1% cream, but the EAG considers it likely that the company would be aware of all such evidence for the intervention and unlikely to have missed any. Therefore, the concerns are noted and would benefit from being addressed if the review is updated or if additional emphasis is placed on sources of non-randomised evidence for comparator treatments, but the EAG considers it unlikely that resolving these issues at this point in time would have led to the consideration of any additional RCTs for inclusion in the evidence base for GPB 1% cream or inclusion in the ITCs against relevant comparators.

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Inclusion criteria	Appendix B.1.3	**Appropriate** The eligibility criteria for inclusion in the clinical SLR outlined in Table 4 of the company submission appendices is slightly broader than the population outlined in the NICE final scope; the SLR is designed to include those with severe primary or secondary axillary hyperhidrosis, while the focus of the NICE final scope and the company's positioning of GPB 1% cream in this appraisal is specifically severe primary axillary hyperhidrosis. Studies in the secondary hyperhidrosis population were later deprioritised in the company's selection of suitable comparator treatment studies for ITCs. In order make the most of evidence that is available but may not completely match this population, criteria were set so that at least 50% of the trial population had to meet each criterion to be included in the SLR (i.e. at least 50% with severe secondary or primary hyperhidrosis, at least 50% with axillary hyperhidrosis and at least 50% adults). The EAG considers the exclusions of populations where there were <50% adults, those with Frey's syndrome and those with compensatory hyperhidrosis to be reasonable. Inclusion and exclusion criteria for interventions are considered to be appropriate and in line with the NICE final scope in terms of the intervention and comparators listed, with any comparator included in trials of these treatments accepted in the SLR. Similarly, no restrictions were placed on outcomes for studies to be included in the SLR and the aim was that randomised and non-randomised studies would be included, with consideration of SLRs and meta-analyses. Inclusion was limited to English language studies.
Screening	Appendices B.1.3 and B.2.1	**Appropriate** Results from all databases were de-duplicated prior to screening in Zotero (open-source reference management software), with each publication then screened against pre-defined eligibility criteria in Microsoft Excel®. Title and abstract screening and full-text screening stages were performed independently by two reviewers, with any discrepancies between reviewers reconciled through consensus or involvement of a third independent reviewer. A PRISMA diagram is provided in Figure 1 of the company submission appendices to show the inclusion and exclusion of studies throughout the screening process. A full list of studies included in the SLR and excluded at title and abstract and full-text screening stages has been provided by the company.
Data extraction	Appendix B.1.4	**Appropriate** Data were extracted by a single reviewer into extraction tables within Microsoft Excel® and the extracted data were verified by a second reviewer. Any discrepancies between reviewers were reconciled by a third reviewer. Where multiple publications on the same study cohort were identified, the primary and secondary publications were linked.

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Tool for quality assessment of included study or studies	Section 2.5 and Appendices B.1.4 and B.2.2.2	**Appropriate but lack of details for non-randomised studies** The Cochrane Risk of Bias (ROB) 2 tool was said to have been used for the quality assessment of RCTs included within the SLR, but copies of these assessments were not provided. Quality assessments using the Centre for Reviews and Dissemination (CRD)'s Guidance for Undertaking Reviews in Healthcare were performed for the RCTs eventually selected for use in the ITCs and are presented in the company submission and appendices. There is no specific mention of how quality was assessed for non-randomised studies included in the SLR, but there is some mention of selecting questionnaires to "comply with NICE standard", which may refer to any non-RCTs. A quality assessment of the non-randomised Hyp1-18/2016 Phase 3b trial for GPB 1% cream has been presented in Section 2.5 of the company submission, but no details were provided as to which checklist was used and whether the same was applied to other non-RCTs included in the SLR.

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CS, company submission; EAG, External Assessment Group; GPB, glycopyrronium bromide; ITC, indirect treatment comparison; NICE, National Institute for Health and Care Excellence; NIHR, National Institute for Health and Care Research; NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT, randomised controlled trial; SLR, systematic literature review.

7.3 Summary of comparator transition probabilities in the model

Table 84. Oral antimuscarinic transition probabilities included in the economic model

		HDSS health state (moving to)			
		1	2	3	4
Baseline to week 4					
HDSS health state (moving from)	1	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]
Baseline to week 8					
HDSS health state (moving from)	1	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]
Baseline to week 12					
HDSS health state	1	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]

	4	[redacted]	[redacted]	[redacted]	[redacted]
Baseline to week 28					
HDSS health state (moving from)	1	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]
Baseline to week 52					
HDSS health state (moving from)	1	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]
Baseline to week 72					
HDSS health state (moving from)	1	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations:					

Table 85. Botulinum toxin A transition probabilities included in the economic model

		HDSS health state (moving to)			
		1	2	3	4
Baseline to week 4					
HDSS health state (moving from)	1	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]
Baseline to week 8					
HDSS health state (moving from)	1	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]
Baseline to week 12					
HDSS health state (moving from)	1	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]
Baseline to week 28					

HDSS health state (moving from)	1	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]
Baseline to week 52					
HDSS health state (moving from)	1	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]
Baseline to week 72					
HDSS health state (moving from)	1	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HDSS, Hyperhidrosis Disease Severity Scale

7.4 Company clarification question scenario analysis results for the primary care and secondary care models

Table 86. Updated Key scenarios using company corrected base case – Primary care model

Scenario description	Vs oral antimuscarinics		
	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Company updated base-case	[redacted]	[redacted]	**Dominant**
Company corrected base case	[redacted]	[redacted]	**Dominant**
B1a. 100% primary care model. GPB 1% cream versus antimuscarinics. Antimuscarinics consists of propantheline bromide only	[redacted]	[redacted]	**Dominant**
Key company scenario			
Relative efficacy of GPB 1% cream vs. botulinum toxin A ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	[redacted]	Dominant
Key EAG requested scenarios			
B2a. Time horizon: 72-weeks	[redacted]	[redacted]	Dominant
B2b, Time horizon: 2 years	[redacted]	[redacted]	Dominant
B3. Background mortality based on ONS life tables from 2017–2019	[redacted]	[redacted]	Dominant
B4. Peak efficacy for botulinum toxin A at 16 weeks	[redacted]	[redacted]	Dominant
B6. 20% Dysport for patients receiving two or more botulinum toxin A procedures	[redacted]	[redacted]	Dominant

Scenario description	Vs oral antimuscarinics		
	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
B11. 100% compliance with GPB 1% cream	[redacted]	[redacted]	Dominant
B12. Price of propantheline bromide set to £20.74	[redacted]	[redacted]	[redacted]
B18. Primary care monitoring assumed for GPB 1% cream/antimuscarinics and no monitoring costs for botulinum toxin A	[redacted]	[redacted]	Dominant
B19a. Treatment duration for antimuscarinics informed by EAG clinical experts (33.3% discontinue treatment at week 4 (no discontinuations prior to that) and thereafter the 2-weekly rate of discontinuation of 0.20%).	[redacted]	[redacted]	[redacted]
B19b. Treatment duration for antimuscarinics informed by EAG clinical experts and a 2-year time horizon	[redacted]	[redacted]	[redacted]
B20b. Treatment discontinuation for botulinum toxin A is applied according to the treatment schedule and assuming only formal discontinuations from Lowe *et al.* 2007	[redacted]	[redacted]	Dominant
B22a. Assuming the same HDSS response as observed for initial therapies for subsequent therapies	[redacted]	[redacted]	[redacted]
B22b. Assuming the same HDSS response as observed for initial therapies for subsequent therapies and a 2-year time horizon	[redacted]	[redacted]	[redacted]
B22bi. Combination of scenarios B19b, B20b and B22b	[redacted]	[redacted]	[redacted]

Abbreviations: Δ, incremental; CQ, clarification question; GPB, Glycopyrronium bromide EAG, External Assessment Group; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; ONS, office of national statistics; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 87. Updated Key scenarios using company corrected base case – Secondary care model

Scenario description	Vs oral antimuscarinics			Vs botulinum toxin A		
	Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Company updated base-case	[redacted]	[redacted]	**Dominant**	[redacted]	[redacted]	**Dominant**
Company corrected base case	[redacted]	[redacted]	**Dominant**	[redacted]	[redacted]	**Dominant**
B14. 100% secondary care model. Comparators consist of oxybutynin 5mg once daily and botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
Key company scenario						
Relative efficacy of GPB 1% cream vs. botulinum toxin A ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Key EAG requested scenarios						
B2a. Time horizon: 72-weeks	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B2b, Time horizon: 2 years	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B3. Background mortality based on ONS life tables from 2017–2019	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B4. Peak efficacy for botulinum toxin A at 16 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B6. 20% Dysport for patients receiving two or more botulinum toxin A procedures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B11. 100% compliance with GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B15. 5% A&G administration for antimuscarinics in the first administration only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B18. Primary care monitoring assumed for GPB 1% cream/antimuscarinics and no monitoring costs for botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Scenario description	Vs oral antimuscarinics			Vs botulinum toxin A		
	Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
B19a. Treatment duration for antimuscarinics informed by EAG clinical experts (33.3% discontinue treatment at week 4 (no discontinuations prior to that) and thereafter the 2-weekly rate of discontinuation of 0.20%).	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B19b. Treatment duration for antimuscarinics informed by EAG clinical experts and a 2-year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B20b. Treatment discontinuation for botulinum toxin A is applied according to the treatment schedule and assuming only formal discontinuations from Lowe *et al.* 2007	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B22a. Assuming the same HDSS response as observed for initial therapies for subsequent therapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B22b. Assuming the same HDSS response as observed for initial therapies for subsequent therapies and a 2-year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B22bi. Combination of scenarios B19b, B20b and B22b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: Δ, incremental; CQ, clarification question; GPB, Glycopyrronium bromide EAG, External Assessment Group; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; ONS, office of national statistics; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Glycopyrronium bromide cream for treating severe primary axillary hyperhidrosis [ID6487]

EAG report addendum

August 2025

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1 Introduction

The External Assessment Group (EAG) has produced this addendum upon request from the National Institute of Health and Care Excellence (NICE) to provide the committee with the cost-effectiveness results for glycopyrronium bromide (GPB) 1% cream for treating severe primary axillary hyperhidrosis using the company's preferred concessionary price of £103.52 for propantheline bromide. Based on data from Community Pharmacy England, the company considered that from February 2024 to July 2025, the price of propantheline bromide has been over £100 due to supply issues.[1] The company selected the January 2025 concessionary price for their base case analyses and the EAG considers that this is representative of the average price across the period from February 2024 to July 2025.

Analyses using the company's preferred concessionary price include the EAG's preferred assumptions for the primary care model, using both the company's preferred utility values and the EAG's alternative utility values, presented in Section 2.

The EAG considers that it is inappropriate to use a concessionary price for propantheline bromide in the model. The NICE manual states that "*for medicines that are mainly prescribed in primary care, base prices on the drugs tariff*".[2] The drug tariff price for propantheline bromide is £20.74.[3] The EAG notes that based on open prescribing data, from 2010 to Feb 2024, the price has been stable at £20.74 or just below.[4] As such, the EAG considers that the drug tariff price is the typical price for propantheline bromide and that a short-term concessionary price should not be used to inform decision-making. Therefore, the EAG has presented the company's base case results, sensitivity and scenario analyses from their clarification response, which used the drug tariff price for propantheline bromide and EAG scenario analyses (Section 5 and Appendix 7.4 of the EAG report) using the drug tariff price in Section 3 of this report.

2 EAG preferred assumptions for the primary care model using the company's preferred concessionary price for propantheline bromide

2.1 Primary care model – company base case utilities

Table 1 presents the cumulative results of the EAG's preferred assumptions using the company's base case utility values. Deterministic and probabilistic results of the scenario are presented in Table 2.

Table 1. Primary care model: cumulative deterministic results using the EAG's preferred model assumptions and the company's base case utility values – GPB 1% cream versus propantheline bromide

Preferred assumption	Exploratory analysis number	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Company base case	-	[redacted]	[redacted]	Dominant
Corrected company base case	-	[redacted]	[redacted]	Dominant
Comparator is propantheline bromide	CQ scenario – B1a	[redacted]	[redacted]	Dominant
2-year time horizon	CQ scenario – B2b	[redacted]	[redacted]	Dominant
Treatment effectiveness of botulinum toxin A wanes after week 16	CQ scenario – B4	[redacted]	[redacted]	Dominant
Botulinum toxin A OR for ≥1-point improvement in the HDSS score assumed to be the same as that for ≥2-point improvement	Company scenario	[redacted]	[redacted]	Dominant
ONS lifetables from 2017-2019	CQ scenario – B3	[redacted]	[redacted]	Dominant
Removal of AEs	EAG scenario 1	[redacted]	[redacted]	Dominant
Administration costs for propantheline bromide: 90% primary care, 10% primary care + A&G services (1st appointment only)	EAG scenario 2	[redacted]	[redacted]	Dominant
Apply consultant cost for first botulinum toxin A administration and nurse 45 minutes for subsequent	EAG scenario 4	[redacted]	[redacted]	Dominant
Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care	EAG scenario 3	[redacted]	[redacted]	Dominant

Preferred assumption	Exploratory analysis number	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
EAG discontinuation rate for antimuscarinics	CQ scenario – B19a	[redacted]	[redacted]	[redacted]
Botulinum toxin A discontinuation rate applied to each administration and only using Lowe *et al.* 2007 discontinuation data.	CQ scenario - B20 (only formal discontinuations from Lowe et al. 2007).	[redacted]	[redacted]	[redacted]
EAG expert view on basket of subsequent treatment	EAG scenario 5	[redacted]	[redacted]	[redacted]
Average weighted utility value for subsequent treatment health state	CQ scenario – B22	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 2. Primary care model - EAG scenario using preferred model assumptions and the company's base case utility values – GPB 1% cream versus propantheline bromide

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Propantheline bromide	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Propantheline bromide	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

2.2 Primary care model – EAG alternative utility values

Table 3 presents the cumulative results of the EAG's preferred assumptions using the EAG's alternative utility values. Deterministic and probabilistic results of the scenario are presented in Table 4.

Table 3. Primary care model: cumulative deterministic results using the EAG's preferred model assumptions and the EAG's alternative utility values – GPB 1% cream versus propantheline bromide

Preferred assumption	Exploratory analysis number	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Company base case	-	[redacted]	[redacted]	Dominant
Corrected company base case	-	[redacted]	[redacted]	Dominant
Comparator is propantheline bromide	CQ scenario – B1a	[redacted]	[redacted]	Dominant
2-year time horizon	CQ scenario – B2b	[redacted]	[redacted]	Dominant
Treatment effectiveness of botulinum toxin A wanes after week 16	CQ scenario – B4	[redacted]	[redacted]	Dominant
Botulinum toxin A OR for ≥1-point improvement in the HDSS score assumed to be the same as that for ≥2-point improvement	Company scenario	[redacted]	[redacted]	Dominant
ONS lifetables from 2017-2019	CQ scenario – B3	[redacted]	[redacted]	Dominant
Removal of AEs	EAG scenario 1	[redacted]	[redacted]	Dominant
Administration costs for propantheline bromide: 90% primary care, 10% primary care + A&G services (1st appointment only)	EAG scenario 2	[redacted]	[redacted]	Dominant
Apply consultant cost for first botulinum toxin A administration and nurse 45 minutes for subsequent	EAG scenario 4	[redacted]	[redacted]	Dominant
Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care	EAG scenario 3	[redacted]	[redacted]	Dominant
EAG discontinuation rate for antimuscarinics	CQ scenario – B19a	[redacted]	[redacted]	[redacted]
Botulinum toxin A discontinuation rate applied to each administration and only using Lowe *et al*. 2007 discontinuation data.	CQ scenario - B20 (only formal discontinuations from Lowe et al. 2007).	[redacted]	[redacted]	[redacted]
EAG expert view on basket of subsequent treatment	EAG scenario 5	[redacted]	[redacted]	[redacted]
Average weighted utility value for subsequent treatment health state	CQ scenario – B22	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 4. Primary care model - EAG scenario using preferred model assumptions and the EAG's alternative utility values – GPB 1% cream versus propantheline bromide

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Propantheline bromide	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Propantheline bromide	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

3 Company and EAG cost-effectiveness results using the drug tariff price for propantheline bromide

3.1 Company's cost effectiveness results

Table 5 and Table 6 presents the pairwise cost-effectiveness results of the company's updated (i.e., post clarification) base case deterministic and probabilistic analyses versus antimuscarinics and botulinum toxin A, respectively.

The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Incremental results from the company's PSA are based on 1,000 simulations.

In the base-case probabilistic analysis of glycopyrronium bromide 1% cream (GPB 1% cream) versus antimuscarinics, GPB 1% cream was considered dominant based on lower incremental costs of [redacted] and an incremental quality-adjusted life-year (QALY) gain of [redacted]. The net health benefit (NHB) based on the probabilistic results is [redacted] at both the £20,000 and £30,000 threshold. A positive NHB implies that overall population health would be increased because of the new intervention.

Table 5. Company's updated base case results (post clarification) versus antimuscarinics

Interventions	Total Costs (£)	Total LY*	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Antimuscarinics	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Probabilistic results							
Antimuscarinics	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: GPB, Glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

*Undiscounted

In the base-case probabilistic analysis of GPB 1% cream versus botulinum toxin A, GPB 1% cream was also considered dominant based on lower incremental costs of [redacted] and an incremental QALY gain of [redacted]. The net health benefit (NHB) based on the probabilistic results is [redacted] at both the £20,000 and £30,000 thresholds.

Table 6. Company's updated base case results (post clarification) versus botulinum toxin A

Interventions	Total Costs (£)	Total LY*	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Probabilistic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: GPB, Glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

*Undiscounted

Based on multiple comparators, the company also provided results of a fully incremental analysis (see Table 26 of the company's follow-up clarification response document). However, the EAG notes that this was conducted incorrectly as the company compared antimuscarinics to botulinum toxin A, despite antimuscarinics being dominated by GPB 1% cream. Therefore, the EAG notes that the results of the fully incremental analysis for botulinum toxin A are the same as in the pairwise comparison of GPB 1% cream versus botulinum toxin A, as shown in Table 6.

Figure 1 and Figure 2 shows PSA scatterplots of GPB 1% cream versus antimuscarinics and botulinum toxin A, respectively, with the corresponding cost-effectiveness acceptability curve (CEAC) is shown in Figure 3.

Figure 1. Scatterplot of PSA estimates on a cost-effectiveness plane of GPB 1% cream versus antimuscarinics (reproduced from Figure 4 of the company follow-up clarification response)

Figure 2. Scatterplot of PSA estimates on a cost-effectiveness plane of GPB 1% cream versus botulinum toxin (reproduced from Figure 4 of the company follow-up clarification response)

Figure 3. Cost-effectiveness acceptability curve (reproduced from Figure 1 of the company follow-up clarification response)

3.1.1 Company's sensitivity analyses

3.1.1.1 One-way sensitivity analysis

The company conducted one-way sensitivity analyses (OWSAs) to assess the impact on the incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) of varying specific parameters in isolation and to identify the main model drivers. The results are illustrated in the tornado diagrams presented Figure 4 and Figure 5 for GPB 1% cream versus antimuscarinics and botulinum toxin A, respectively.

As shown in the figures below, varying utility values for health states HDSS 2–4 had the largest impact on the NMB. The EAG notes that the values used in the OWSA for utility values result in wide confidence intervals due to high variation around the mean. Therefore, the EAG considers that this may be the reason for the large impact on the results.

Figure 4. Tornado plot for antimuscarinics (reproduced from Figure 6 of the company's follow-up clarification response)

Figure 5. Tornado plot for botulinum toxin A (reproduced from Figure 8 of the company's follow-up clarification response)

3.1.1.2 Scenario analysis

The company undertook an extensive series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters, presented in Table 7. In addition, the company conducted several additional scenario analyses requested by the EAG, also presented in Table 7.

As shown in Table 7, GPB 1% cream remained the dominant treatment in all but two of the company's scenario analyses, in which the resulting ICER was less than £1,000.

The EAG prefers the cost-effectiveness results to be presented by care setting. Additionally, the EAG made corrections to the company model. As such, the EAG's re-ran only the company's key EAG-requested clarification question (CQ) scenarios for the primary care setting (CQ scenario B1a) and the secondary care setting (CQ scenario B14) as the EAG considers they are the most important scenarios. Only one of the company's scenarios was included in the EAG's preferred assumptions (relative efficacy of GPB 1% cream vs. botulinum toxin A ≥1 HDSS score assumed the same as ≥2 HDSS score), and this is also included as part of the EAG's reanalysis of the company's key scenarios. Results of the EAG's reanalysis of key scenarios are presented in the Appendix.

Table 7. Company updated scenario analysis, reproduced from the company's model, deterministic

Scenario description	Vs oral antimuscarinics			Vs botulinum toxin A		
	Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Company updated base-case	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Time horizon: 4-years	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Time horizon: 5-years	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Time horizon: 10-years	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Half cycle correction: excluded	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Discount rate: 0% costs and 0% outcomes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Baseline characteristics: FASa	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Baseline characteristics: PPSb	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Baseline GPB 1% cream efficacy: PPSb	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Relative efficacy of GPB 1% cream vs. antimuscarinics based on PPSa	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Relative efficacy of GPB 1% cream vs. antimuscarinics based on Wade *et al.* 2017	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Relative efficacy of GPB 1% cream vs. botulinum toxin A based on PPSa	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Relative efficacy of GPB 1% cream vs. botulinum toxin A based on Wade *et al.* 2017	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Relative efficacy of GPB 1% cream vs. botulinum toxin A ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Dose of botulinum toxin A assumed 150U	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant

Scenario description	Vs oral antimuscarinics			Vs botulinum toxin A		
	Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Dose of botulinum toxin A assumed combined of 100U and 150U	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Relative efficacy for 2+ botulinum toxin A procedures based on Lowe et al. (2007)	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Relative efficacy for 2+ botulinum toxin A procedures based on a 10% reduction in OR	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Relative efficacy for 2+ botulinum toxin A procedures based on a 20% reduction in OR	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Maximum botulinum toxin A efficacy achieved at week 8	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Maximum botulinum toxin A efficacy achieved at week 12	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
1.8 botulinum procedures per year	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Cost of propantheline bromide of £20.74	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Dose per day of oxybutynin of 12.5mg	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Dose intensity for oral antimuscarinics assumed equal to GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Increase in discontinuation rate with GPB 1% cream of 10%	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Increase in discontinuation rate with GPB 1% cream of 20%	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Source of discontinuation for antimuscarinics from Millan-Cayetano *et al.* 2016	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Discontinuation for botulinum toxin A assumed as only those who were formally discontinued	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Discontinuation for botulinum toxin A assumed as those who were formally discontinued and no further treatment	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant

Scenario description	Vs oral antimuscarinics			Vs botulinum toxin A		
	Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
EAG requested scenarios						
B1a. 100% primary care model. GPB 1% cream versus antimuscarinics. Antimuscarinics consists of propantheline bromide only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A
B1b. 100% secondary care model. Comparators consist of oxybutynin 2.5mg (three times daily) and botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B2a. Time horizon: 72-weeks	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B2b, Time horizon: 2 years	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B3. Background mortality based on ONS life tables from 2017–2019	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B4. Peak efficacy for botulinum toxin A at 16 weeks	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B6. 20% Dysport for patients receiving two or more botulinum toxin A procedures	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B7. 0% non-axillary sweating adverse event for botulinum toxin A	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B11. 100% compliance with GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B14. 100% secondary care model. Comparators consist of oxybutynin 5mg once daily and botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B15. 5% A&G administration for antimuscarinics in the first administration only	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B16. Non-half-cycle-adjusted monitoring appointments for botulinum toxin A	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B17. Cost of £535 for the administration of botulinum toxin	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant

Scenario description	Vs oral antimuscarinics			Vs botulinum toxin A		
	Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
B18. Primary care monitoring assumed for GPB 1% cream/antimuscarinics and no monitoring costs for botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B19a. Treatment duration for antimuscarinics informed by EAG clinical experts (33.3% discontinue treatment at week 4 (no discontinuations prior to that) and thereafter the 2-weekly rate of discontinuation of 0.20%).	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B19b. Treatment duration for antimuscarinics informed by EAG clinical experts and a 2-year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B20a. Treatment discontinuation for botulinum toxin A is applied according to the treatment schedule	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B20b. Treatment discontinuation for botulinum toxin A is applied according to the treatment schedule and assuming only formal discontinuations from Lowe *et al.* 2007	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
B22a. Assuming the same HDSS response as observed for initial therapies for subsequent therapies	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]
B22b. Assuming the same HDSS response as observed for initial therapies for subsequent therapies and a 2-year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B22bi. Combination of scenarios B19b, B20b and B22b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
B24a. Subsequent therapy distribution based on EAG's clinical feedback and assuming the same HDSS response as observed for initial therapies for subsequent therapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario description	Vs oral antimuscarinics			Vs botulinum toxin A		
	Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
B24b. Scenario B24a plus two-year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: Δ, incremental; CQ, clarification question; GPB, Glycopyrronium bromide EAG, External Assessment Group; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; ONS, office of national statistics; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west

3.2 EAG additional analyses

3.2.1 Model corrections

The EAG identified the following errors and updates needed in the economic model:

- Since the original company submission, the BNF price for oxybutynin has been updated to £1.50 and this has been updated in the model.
- A lower price of £71.35 for oral GPB was available from Drugs and pharmaceutical electronic market information tool (eMIT), and this has been updated in the model.
- In their clarification response, the company corrected hard-coded values for total costs of subsequent treatments in the model and instead derived the values from the model traces. However, the formula incorrectly references the wrong lookup value and so the model still relied on the hardcoded values. The EAG corrected the formula, located in the "Costs" tab, cells D62:D66 (changed from CQ_B22, to CQ_B21).
- In the economic model, the company reported the AE values for the 75U botulinum toxin A dose rather than the 50U dose from Lowe *et al*. 2007. The AE values should be 12% for injection site pain, 5% for injection site bleeding and 10% for non-axillary sweating. The EAG has corrected the data in the model.

The corrected company base results for oral antimuscarinics and botulinum toxin A are presented in Table 8 and Table 9, respectively.

Table 8. Corrected company's updated base case results (post clarification) versus antimuscarinics

Interventions	Total Costs (£)	Total LY*	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Antimuscarinics	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Antimuscarinics	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: GPB, Glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

*Undiscounted

Table 9. Corrected company's updated base case results (post clarification) versus botulinum toxin A

Interventions	Total Costs (£)	Total LY*	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Probabilistic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: GPB, Glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

*Undiscounted

3.2.2 EAG's exploratory analyses using the company's base case

Results of the EAG's scenario analysis around the corrected company base case are presented in Table 10 and Table 11 for the primary care model and secondary care model, respectively.

Table 10. Results of EAG's deterministic exploratory analyses using company's base case – primary care model

Exploratory analysis number	Scenario applied to company's base case	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case	-	[redacted]	[redacted]	**Dominant**
Corrected company base case	-	[redacted]	[redacted]	[redacted]
0	**Comparator is propantheline bromide (CQ B1a scenario)**	[redacted]	[redacted]	[redacted]
1	Exclusion of costs and disutilities associated with AEs	[redacted]	[redacted]	[redacted]
2	Administration costs for propantheline bromide: 90% primary care, 10% primary care + A&G services (1st appointment only)	[redacted]	[redacted]	[redacted]
3	Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care.	[redacted]	[redacted]	[redacted]

Exploratory analysis number	Scenario applied to company's base case	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
4	1st administration of botulinum toxin A given by consultant and then cost of 45 minutes of Band 6 nurse time only for all subsequent administrations. Excludes additional monitoring costs for botulinum toxin A.	[redacted]	[redacted]	[redacted]
5a	EAG's clinical expert advice on basket of subsequent treatment for the primary care model	[redacted]	[redacted]	[redacted]
5b	EAG's clinical expert advice on basket of subsequent treatment for the primary care model + weighted average utility value for the subsequent treatment health state	[redacted]	[redacted]	[redacted]
7	Scenario 5b + two-year time horizon	[redacted]	[redacted]	[redacted]
8	Mapped EQ-5D-3L utility values for the HDSS health states	[redacted]	[redacted]	[redacted]
9	Mapped EQ-5D-3L utility values for the HDSS health states + weighted average utility value for the subsequent treatment health state.	[redacted]	[redacted]	[redacted]
10	Scenario 5b + 8	[redacted]	[redacted]	[redacted]
11	Scenario 9 and two-year time horizon	[redacted]	[redacted]	[redacted]
12	Scenario 5b + 11	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 11. Results of EAG's deterministic exploratory analyses using company's base case – secondary care model

Exploratory analysis number	Scenario applied to company's base case	Vs oral antimuscarinics			Vs botulinum toxin A		
		Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Company base case	**-**	[redacted]	[redacted]	**Dominant**	[redacted]	[redacted]	**Dominant**
Corrected company base case	**-**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
0	**Comparators are modified-release oxybutynin 5 mg and botulinum toxin A (CQ scenario B14)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
1	Exclusion of costs and disutilities associated with AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
3	Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
4	1st administration of botulinum toxin A given by consultant and then cost of 45 minutes of Band 6 nurse time only for all subsequent administrations. Excludes additional monitoring costs for botulinum toxin A.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
6	EAG's clinical expert advice on basket of subsequent treatment for the primary care model + weighted average utility value for the subsequent treatment health state (CQ scenario B24)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	Scenario 6 + two-year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
8	Mapped EQ-5D-3L utility values for the HDSS health states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
9	Mapped EQ-5D-3L utility values for the HDSS health states + weighted average utility value for the subsequent treatment health state.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	Scenario 6 + 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	Scenario 9 and two-year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Exploratory analysis number	Scenario applied to company's base case	Vs oral antimuscarinics			Vs botulinum toxin A		
		Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
12	Scenario 6 + 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: Δ, incremental; AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

3.2.3 EAG preferred assumptions

As discussed in the EAG report, the EAG does not consider either the company's base case EQ-5D-5L utility values or the EAG's estimated EQ-5D-5L values mapped to EQ-5D-3L to be appropriate for an EAG base-case analysis. As such, the EAG has provided the following scenarios instead of an EAG base case:

- Primary care model using the company's base case EQ-5D-5L utility values and the EAG's other preferred model assumptions.
- Secondary care model using the company's base case EQ-5D-5L utility values and the EAG's other preferred model assumptions.
- Primary care model using the EAG's alternative EQ-5D-3L mapped utility values and the EAG's other preferred model assumptions.
- Secondary care model using the EAG's alternative EQ-5D-3L mapped utility values and the EAG's other preferred model assumptions.

3.2.3.1 Primary care model – company base case utilities

Table 12 presents the cumulative results of the EAG's preferred assumptions using the company's base case utility values. Deterministic and probabilistic results of the scenario are presented in Table 13.

Table 12. Primary care model: cumulative deterministic results using the EAG's preferred model assumptions and the company's base case utility values – GPB 1% cream versus propantheline bromide

Preferred assumption	Exploratory analysis number	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Company base case	-	[redacted]	[redacted]	Dominant
Corrected company base case	-	[redacted]	[redacted]	[redacted]
Comparator is propantheline bromide	CQ scenario – B1a	[redacted]	[redacted]	[redacted]
2-year time horizon	CQ scenario – B2b	[redacted]	[redacted]	Dominant
Treatment effectiveness of botulinum toxin A wanes after week 16	CQ scenario – B4	[redacted]	[redacted]	Dominant
Botulinum toxin A OR for ≥1-point improvement in the HDSS score assumed to be the same as that for ≥2-point improvement	Company scenario	[redacted]	[redacted]	Dominant

Preferred assumption	Exploratory analysis number	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
ONS lifetables from 2017-2019	CQ scenario – B3	[redacted]	[redacted]	Dominant
Removal of AEs	EAG scenario 1	[redacted]	[redacted]	Dominant
Administration costs for propantheline bromide: 90% primary care, 10% primary care + A&G services (1st appointment only)	EAG scenario 2	[redacted]	[redacted]	Dominant
Apply consultant cost for first botulinum toxin A administration and nurse 45 minutes for subsequent	EAG scenario 4	[redacted]	[redacted]	Dominant
Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care	EAG scenario 3	[redacted]	[redacted]	Dominant
EAG discontinuation rate for antimuscarinics	CQ scenario – B19a	[redacted]	[redacted]	[redacted]
Botulinum toxin A discontinuation rate applied to each administration and only using Lowe *et al.* 2007 discontinuation data.	CQ scenario - B20 (only formal discontinuations from Lowe et al. 2007).	[redacted]	[redacted]	[redacted]
EAG expert view on basket of subsequent treatment	EAG scenario 5	[redacted]	[redacted]	[redacted]
Average weighted utility value for subsequent treatment health state	CQ scenario – B22	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 13. Primary care model - EAG scenario using preferred model assumptions and the company's base case utility values – GPB 1% cream versus propantheline bromide

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Propantheline bromide	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Propantheline bromide	[redacted]	[redacted]	[redacted]	-	-	-	-

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

3.2.3.2 Primary care model – EAG alternative utility values

Table 14 presents the cumulative results of the EAG's preferred assumptions using the EAG's alternative utility values. Deterministic and probabilistic results of the scenario are presented in Table 15.

Table 14. Primary care model: cumulative deterministic results using the EAG's preferred model assumptions and the EAG's alternative utility values – GPB 1% cream versus propantheline bromide

Preferred assumption	Exploratory analysis number	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Company base case	-	[redacted]	[redacted]	Dominant
Corrected company base case	-	[redacted]	[redacted]	[redacted]
Comparator is propantheline bromide	CQ scenario – B1a	[redacted]	[redacted]	[redacted]
2-year time horizon	CQ scenario – B2b	[redacted]	[redacted]	Dominant
Treatment effectiveness of botulinum toxin A wanes after week 16	CQ scenario – B4	[redacted]	[redacted]	Dominant
Botulinum toxin A OR for ≥1-point improvement in the HDSS score assumed to be the same as that for ≥2-point improvement	Company scenario	[redacted]	[redacted]	Dominant
ONS lifetables from 2017-2019	CQ scenario – B3	[redacted]	[redacted]	Dominant
Removal of AEs	EAG scenario 1	[redacted]	[redacted]	Dominant
Administration costs for propantheline bromide: 90% primary care, 10% primary care + A&G services (1st appointment only)	EAG scenario 2	[redacted]	[redacted]	Dominant

Preferred assumption	Exploratory analysis number	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Apply consultant cost for first botulinum toxin A administration and nurse 45 minutes for subsequent	EAG scenario 4	[redacted]	[redacted]	Dominant
Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care	EAG scenario 3	[redacted]	[redacted]	Dominant
EAG discontinuation rate for antimuscarinics	CQ scenario – B19a	[redacted]	[redacted]	[redacted]
Botulinum toxin A discontinuation rate applied to each administration and only using Lowe *et al*. 2007 discontinuation data.	CQ scenario - B20 (only formal discontinuations from Lowe et al. 2007).	[redacted]	[redacted]	[redacted]
EAG expert view on basket of subsequent treatment	EAG scenario 5	[redacted]	[redacted]	[redacted]
Average weighted utility value for subsequent treatment health state	CQ scenario – B22	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 15. Primary care model - EAG scenario using preferred model assumptions and the EAG's alternative utility values – GPB 1% cream versus propantheline bromide

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Propantheline bromide	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Propantheline bromide	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

3.2.3.3 Secondary care model - company base case utilities

Table 16 presents the cumulative results of the EAG's preferred assumptions using the company's base case utility values. Deterministic and probabilistic results of the scenario for modified-release oxybutynin and botulinum toxin A are presented in Table 17 and Table 18, respectively. Fully incremental results are presented in Table 19.

Table 16. Secondary care model: cumulative deterministic results using the EAG's preferred model assumptions and the company's base case utility values

Preferred assumption	Exploratory analysis number	Vs modified-release oxybutynin			Vs botulinum toxin A		
		Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Company base case	-	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Corrected company base case	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Comparators are modified-release oxybutynin 5 mg and botulinum toxin A	CQ scenario – B14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
2-year time horizon	CQ scenario – B2b	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Treatment effectiveness of botulinum toxin A wanes after week 16	CQ scenario – B4	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Botulinum toxin A OR for ≥1-point improvement in the HDSS score assumed to be the same as that for ≥2-point improvement	Company scenario	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
ONS lifetables from 2017-2019	CQ scenario – B3	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Removal of AEs	EAG scenario 1	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Apply consultant cost for first botulinum toxin A administration and nurse 45 minutes for subsequent	EAG scenario 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Preferred assumption	Exploratory analysis number	Vs modified-release oxybutynin			Vs botulinum toxin A		
		Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care	EAG scenario 3	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
EAG discontinuation rate for antimuscarinics	CQ scenario – B19a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Botulinum toxin A discontinuation rate applied to each administration and only using Lowe *et al*. 2007 discontinuation data.	CQ scenario - B20 (only formal discontinuations from Lowe et al. 2007).	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG expert view on basket of subsequent treatment and average weighted utility value for subsequent treatment health state	CQ scenario – B24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 17. Secondary care model - EAG scenario using preferred model assumptions and the company's base case utility values – GPB 1% cream versus modified-release oxybutynin

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Modified-release oxybutynin	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Modified-release oxybutynin	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 18. Secondary care model - EAG scenario using preferred model assumptions and the company's base case utility values – GPB 1% cream versus botulinum toxin A

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 19. Fully incremental analysis (based on PSA results) – secondary care model, company base case utility values

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
GPB 1% cream	[redacted]	[redacted]	[redacted]	-	-	-	-

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Modified-release oxybutynin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

3.2.3.4 Secondary care model – EAG alternative utility values

Table 20 presents the cumulative results of the EAG's preferred assumptions using the company's base case utility values. Deterministic and probabilistic results of the scenario for modified-release oxybutynin and botulinum toxin A are presented in Table 21 and Table 22, respectively. Fully incremental results are presented in Table 23.

Table 20. Secondary care model: cumulative deterministic results using the EAG's preferred model assumptions and the EAG's alternative utility values

Preferred assumption	Exploratory analysis number	Vs modified-release oxybutynin			Vs botulinum toxin A		
		Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Company base case	-	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Corrected company base case	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Comparators are modified-release oxybutynin 5 mg and botulinum toxin A	CQ scenario – B14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
2-year time horizon	CQ scenario – B2b	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Treatment effectiveness of botulinum toxin A wanes after week 16	CQ scenario – B4	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Botulinum toxin A OR for ≥1-point improvement in the HDSS score assumed to be the same as that for ≥2-point improvement	Company scenario	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
ONS lifetables from 2017-2019	CQ scenario – B3	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Removal of AEs	EAG scenario 1	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Apply consultant cost for first botulinum toxin A administration and nurse 45 minutes for subsequent	EAG scenario 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Preferred assumption	Exploratory analysis number	Vs modified-release oxybutynin			Vs botulinum toxin A		
		Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY	Cumulative Incremental costs (£)	Cumulative Incremental QALYs	Cumulative ICER £/QALY
Annual monitoring of patients for GPB 1% cream and antimuscarinics and all appointments take place in primary care	EAG scenario 3	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
EAG discontinuation rate for antimuscarinics	CQ scenario – B19a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Botulinum toxin A discontinuation rate applied to each administration and only using Lowe *et al*. 2007 discontinuation data.	CQ scenario - B20 (only formal discontinuations from Lowe et al. 2007).	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG expert view on basket of subsequent treatment and average weighted utility value for subsequent treatment health state	CQ scenario – B24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; A&G, advice and guidance; CQ, clarification question; EAG, External Assessment Group; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 21. Secondary care model - EAG scenario using preferred model assumptions and the EAG's alternative utility values – GPB 1% cream versus modified-release oxybutynin

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Modified-release oxybutynin	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Modified-release oxybutynin	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 22. Secondary care model - EAG scenario using preferred model assumptions and the EAG's alternative utility values – GPB 1% cream versus botulinum toxin A

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Botulinum toxin A	[redacted]	[redacted]	[redacted]	-	-	-	-
GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

Table 23. Fully incremental analysis (based on PSA results) – secondary care model, EAG alternative utility values

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
GPB 1% cream	[redacted]	[redacted]	[redacted]	-	-	-	-

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Modified-release oxybutynin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.

4 References

1. Community Pharmacy England. Price concession archive. 2025. Available from: https://cpe.org.uk/funding-and-reimbursement/reimbursement/price-concessions/archive/. Date accessed: August 2025.
2. National Institue for Health and Care Excellence. NICE health technology evaluations: the manual [PMG36], 2022. Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741. Date accessed: 26/06/2025.
3. National Institute for Health and Care Excellence. British National Formulary. 2025. Available from: https://bnf.nice.org.uk/. Date accessed: August 2025.
4. OpenPrescribing. Tariff prices for Propantheline bromide 15mg tablets. 2025. Available from: https://openprescribing.net/tariff/?codes=0102000Y0AAAFAF. Date accessed: August 2025.
5. Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in healthcare. *Available at https://wwwyorkacuk/media/crd/Systematic_Reviewspdf (Accessed 21 March 2016)* 2011.

5 Appendix - Company clarification question scenario analysis results for the primary care and secondary care models

Table 24. Updated Key scenarios using company corrected base case – Primary care model

Scenario description	Vs oral antimuscarinics		
	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Company updated base case	[redacted]	[redacted]	[redacted]
Company corrected base case	[redacted]	[redacted]	[redacted]
B1a. 100% primary care model. GPB 1% cream versus antimuscarinics. Antimuscarinics consists of propantheline bromide only	[redacted]	[redacted]	[redacted]
Key company scenario			
Relative efficacy of GPB 1% cream vs. botulinum toxin A ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	[redacted]	[redacted]
Key EAG requested scenarios			
B2a. Time horizon: 72-weeks	[redacted]	[redacted]	[redacted]
B2b, Time horizon: 2 years	[redacted]	[redacted]	[redacted]
B3. Background mortality based on ONS life tables from 2017–2019	[redacted]	[redacted]	[redacted]
B4. Peak efficacy for botulinum toxin A at 16 weeks	[redacted]	[redacted]	[redacted]
B6. 20% Dysport for patients receiving two or more botulinum toxin A procedures	[redacted]	[redacted]	[redacted]
B11. 100% compliance with GPB 1% cream	[redacted]	[redacted]	[redacted]
B18. Primary care monitoring assumed for GPB 1% cream/antimuscarinics and no monitoring costs for botulinum toxin A	[redacted]	[redacted]	[redacted]
B19a. Treatment duration for antimuscarinics informed by EAG clinical experts (33.3% discontinue treatment at week 4 (no discontinuations prior to that) and thereafter the 2-weekly rate of discontinuation of 0.20%).	[redacted]	[redacted]	[redacted]
B19b. Treatment duration for antimuscarinics informed by EAG clinical experts and a 2-year time horizon	[redacted]	[redacted]	[redacted]
B20b. Treatment discontinuation for botulinum toxin A is applied according to the treatment schedule and assuming only formal discontinuations from Lowe *et al.* 2007	[redacted]	[redacted]	[redacted]
B22a. Assuming the same HDSS response as observed for initial therapies for subsequent therapies	[redacted]	[redacted]	[redacted]
B22b. Assuming the same HDSS response as observed for initial therapies for subsequent therapies and a 2-year time horizon	[redacted]	[redacted]	[redacted]

Scenario description	Vs oral antimuscarinics		
	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
B22bi. Combination of scenarios B19b, B20b and B22b	[redacted]	[redacted]	[redacted]

Abbreviations: Δ, incremental; CQ, clarification question; GPB, Glycopyrronium bromide EAG, External Assessment Group; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; ONS, office of national statistics; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Table 25. Updated Key scenarios using company corrected base case – Secondary care model

Scenario description	Vs oral antimuscarinics			Vs botulinum toxin A		
	Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
Company updated base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company corrected base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B14. 100% secondary care model. Comparators consist of oxybutynin 5mg once daily and botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key company scenario						
Relative efficacy of GPB 1% cream vs. botulinum toxin A ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key EAG requested scenarios						
B2a. Time horizon: 72-weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B2b, Time horizon: 2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B3. Background mortality based on ONS life tables from 2017–2019	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B4. Peak efficacy for botulinum toxin A at 16 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B6. 20% Dysport for patients receiving two or more botulinum toxin A procedures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B11. 100% compliance with GPB 1% cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B15. 5% A&G administration for antimuscarinics in the first administration only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B18. Primary care monitoring assumed for GPB 1% cream/antimuscarinics and no monitoring costs for botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario description	Vs oral antimuscarinics			Vs botulinum toxin A		
	Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)
B19a. Treatment duration for antimuscarinics informed by EAG clinical experts (33.3% discontinue treatment at week 4 (no discontinuations prior to that) and thereafter the 2-weekly rate of discontinuation of 0.20%).	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B19b. Treatment duration for antimuscarinics informed by EAG clinical experts and a 2-year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B20b. Treatment discontinuation for botulinum toxin A is applied according to the treatment schedule and assuming only formal discontinuations from Lowe *et al.* 2007	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B22a. Assuming the same HDSS response as observed for initial therapies for subsequent therapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B22b. Assuming the same HDSS response as observed for initial therapies for subsequent therapies and a 2-year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B22bi. Combination of scenarios B19b, B20b and B22b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Δ, incremental; CQ, clarification question; GPB, Glycopyrronium bromide EAG, External Assessment Group; HDSS, Hyperhidrosis Disease Severity Scale; ICER, incremental cost-effectiveness ratio; ONS, office of national statistics; OR, odds ratio; QALY, quality-adjusted life-year; SW, south-west.

Single Technology Appraisal

Glycopyrronium bromide cream for treating severe primary axillary hyperhidrosis [ID6487]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 8 August** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Factual inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 26, 99: "For patients in the comparator arms of the model, [redacted] years are spent in the subsequent treatment health state." Page 33, 124: "…and then spend approximately [redacted] years in the subsequent treatment health state only accruing the utility value associated with their baseline HDSS score. Page 33: "…and spend approximately [redacted] years in the subsequent treatment health state." Page 168: "…that patients in all treatment arms spend most of the model time horizon in the subsequent health state ([redacted] years for GPB 1% cream, ~[redacted] years for the comparators)."	Page 26, 99: "For patients in the comparator arms of the model, [redacted] years are spent in the subsequent treatment health state." Page 33, 124: "…and then spend approximately [redacted] years in the subsequent treatment health state only accruing the utility value associated with their baseline HDSS score. Page 33: "…and spend approximately [redacted] years in the subsequent treatment health state." Page 168: "…that patients in all treatment arms spend most of the model time horizon in the subsequent health state ([redacted] years for GPB 1% cream, [redacted] years for the comparators)."	Incorrect number of years spent in the subsequent treatment health states for the comparator arms and GPB 1% cream.	The EAG has amended the report to more accurately reflect the life years data.
Page 64: "The company also provided details of a related unpublished Phase 1b study (NCT03037788)[15, 16]"	The company also provided details of a related Phase 1b study (NCT03037788)[15, 16]	This study is in fact published; please see this reference C. Masur, M. Soeberdt, A. Kilic, U. Knie, C. Abels, Safety and efficacy of topical formulations containing	Thank you for highlighting this publication. The EAG report has been amended to remove the word

		0·5, 1 and 2% glycopyrronium bromide in patients with primary axillary hyperhidrosis: a randomized, double-blind, placebo-controlled study, *British Journal of Dermatology*, Volume 182, Issue 1, 1 January 2020, Pages 229–231, https://doi.org/10.1111/bjd.18234	'unpublished' from the sentence highlighted by the company.
Page 30, 102, 119: "The results of the ITC demonstrated that both oral antimuscarinics and botulinum toxin A are [redacted]" Page 102: "The ORs for oral antimuscarinics and botulinum toxin A indicate that both treatments are [redacted]" Page 123: "This is a particular problem as both oral antimuscarinics and botulinum toxin A were found to be [redacted] but are…" Page 167: "…the company's indirect treatment comparison estimated that	Page 30, 102, 119: "The results of the ITC suggested that oral antimuscarinics [redacted] and that botulinum toxin is [redacted]." Page 102: "The ORs suggested that oral antimuscarinics [redacted] and that botulinum toxin is [redacted]." Page 123: "This is a particular that oral antimuscarinics [redacted] and that botulinum toxin is [redacted] but are…"	The current wording implies that both oral antimuscarinics and botulinum toxin A are more effective than GPB 1% cream. While the indirect treatment comparisons (ITCs) show a numerical advantage for oral antimuscarinics, this difference is not statistically significant.	The EAG has amended the wording to "[redacted]" to capture the lack of statistical significance of the ITC results.

both oral antimuscarinics and botulinum toxin A are [redacted]."	Page 167: "the company's indirect treatment comparison suggested that oral antimuscarinics [redacted] and that botulinum toxin is [redacted]."		
Page 71, Table 32, Column 1, Row 11: "Week 12 LSmeans (95% CI)"	**Day 29** LSmeans (95% CI)	Incorrect timescale	Thank you for highlighting this error. The text in the EAG report has been amended to "Day 29".
Page 83, "The EAG was unable to validate the data for ≥1 point improvement in HDSS score from baseline to Day 29 for the FASa population reported in CS, Table 12 and notes that the Phase 3b data were supplied by the company in response to a clarification question for the source of these data rather than the requested data from Phase 3a (A20). The EAG therefore cannot confirm the accuracy of the ITC for ≥1 point improvement in HDSS score."	The Company apologises for the confusion. Data on the proportion of patients achieving a ≥1-point improvement in HDSS score from baseline to Day 29 in the FASa population are reported in Table 4 of Abels et al. (2021).	The current wording ("*The EAG therefore cannot confirm the accuracy of the ITC for ≥1 point improvement in HDSS score*") may be misleading, as it suggests that the data are either unavailable or unreliable. However, the relevant data for this outcome are reported in Abels et al. (2021). We recommend revising the statement to reflect the availability of data,	Thank you for highlighting the source of these data. The EAG has now validated the data for ≥1 point improvement in HDSS score from baseline to Day 29 for the FASa population reported in CS, Table 12 and

		rather than implying a lack of accuracy.	updated the EAG report to remove the text highlighted by the company.
Page 100: “The company stated that more complex methods for modelling subsequent treatments were explored such as using a payoff method, but they considered that if patients had failed second-line treatment, their underlying PAHH may be more difficult to treat and as such are unlikely to experience the same level of benefit as patients who are treated earlier, but are expected to incur the costs of treatment.”	Revise the description of the company’s approach to modelling subsequent treatments to clarify the rationale for not adopting a more complex payoff approach and to better reflect the justification for the simplified assumption used in the model.	The current wording implies that the decision not to pursue a more complex payoff modelling approach was based solely on clinical reasoning regarding disease progression. However, while the company did explore more complex methods (such as the payoff approach) the decision not to pursue this was primarily due to the lack of robust data to support such modelling in this setting. The simplified assumption used instead, i.e., that patients may not derive the same level of benefit from treatment as they move through successive lines of therapy, is consistent	Thank you for highlighting this oversight. The EAG report has been amended to include the following, “The company stated that more complex methods for modelling subsequent treatments were explored such as using a payoff method but considered there was a lack of robust data available to support this modelling approach”.

		with the clinical perspective noted, but was also chosen to ensure model feasibility and transparency in the context of limited evidence. The proposed revision ensures that both the practical limitations and the clinical rationale behind the modelling approach are clearly represented.	
Global: “oral muscarinics”	“oral **anti**muscarinics”	‘Oral muscarinics’ and ‘oral antimuscarinics’ refer to distinct classes of drugs; please update the wording to ‘oral antimuscarinics’ to ensure accuracy.	Thank you for highlighting these errors. The EAG report has been corrected
Table 49, Page 112, cost of propantheline bromide “£20.74”	In response to the EAG’s Clarification Question B12, the company updated its base case to reflect the lowest Drug Tariff price for propantheline bromide (£20.74). The original base case had used a higher cost of £103.52, based on recent supply shortages of the lower-cost formulation and evidence that, as a result, higher-cost	The amendment is proposed to ensure that the base case reflects current UK clinical practice and the actual cost incurred by the NHS for propantheline bromide. Continuing to use the lower price	Based on advice from NICE, the EAG has updated Section 1 and 5 of the EAG report. The EAG has also updated its description and

<table>
<tr>
<td></td>
<td>packs were being used in UK clinical practice.

The company made the update in line with the EAG’s request, as primary care data for England from March 2025 indicated a temporary return to the lower price of £20.74. However, more recent data from April to June 2025 (Table 1) show that this reduction was short-lived, and the cost of propantheline bromide in UK clinical practice has reverted to above £100.

We informed NICE of this on 6 August 2025 and confirmed our intention to reinstate the £103.52 unit cost in the company’s base case. NICE advised that this revised base case should be included as part of this factual accuracy response. The revised base case is presented at the end of this document.

Table 1: Price trends for propantheline bromide
<table>
<tr><th>Month</th><th>Drug</th><th>Pack size</th><th>Price concession</th><th>VMPP SNOMED code</th></tr>
<tr><td>Jun-25</td><td>Propantheline bromide 15mg tablets</td><td>112</td><td>£104.99</td><td>1180711000001106</td></tr>
<tr><td>May-25</td><td>Propantheline bromide</td><td>112</td><td>£104.49</td><td>1180711000001106</td></tr>
</table>
</td>
<td>would underestimate the true cost to the NHS.

The company's original assumption of £103.52 was based on observed market dynamics during a period of sustained supply shortages, and these conditions now appear to have resumed.</td>
<td>critique in Sections 4.2.7.1 and 4.2.7.2. The EAG has also produced an addendum to the EAG report with the EAG’s base case using the concessionary price as well as company and EAG cost-effectiveness results, sensitivity and scenario analyses using the drug tariff price.</td>
</tr>
</table>

		15mg tablets				
	Apr-25	Propantheline bromide 15mg tablets	112	£98.16	11807110000011106	
	Feb-25	Propantheline bromide 15mg tablets	112	£103.33	11807110000011106	
	Jan-25	Propantheline bromide 15mg tablets	112	£103.52	11807110000011106	
	Dec-24	Propantheline bromide 15mg tablets	112	£103.66	11807110000011106	
	Nov-24	Propantheline bromide 15mg tablets	112	£103.38	11807110000011106	
	Oct-24	Propantheline bromide 15mg tablets	112	£103.50	11807110000011106	
	Sep-24	Propantheline bromide 15mg tablets	112	£103.50	11807110000011106	
	Aug-24	Propantheline bromide 15mg tablets	112	£103.99	11807110000011106	

	Jul-24	Propantheline bromide 15mg tablets	112	£104.29	1180711000001106		
	Jun-24	Propantheline bromide 15mg tablets	112	£107.49	1180711000001106		
	May-24	Propantheline bromide 15mg tablets	112	£100.61	1180711000001106		
	Apr-24	Propantheline bromide 15mg tablets	112	£100.61	1180711000001106		
	Mar-24	Propantheline bromide 15mg tablets	112	£100.61	1180711000001106		
	Feb-24	Propantheline bromide 15mg tablets	112	£108.44	1180711000001106		
	Source: Community Pharmacy England's price concession archive, accessed August 2025[1]						

Issue 2 Wording changes to clarify

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 22: "Prior to oral anticholinergic medication	"As an alternative to oral anticholinergic medication	To clarify where GPB 1% cream will be positioned as the	Not a factual inaccuracy. No change required. Figure 2 of the CS presents the position of GPB 1%

(antimuscarinics) and botulinum toxin type A in secondary care."	(antimuscarinics) and prior to botulinum toxin type A in secondary care."	current wording in the EAG report is unclear	cream (the orange box) before oral anticholinergics and botulinum toxin A.
Page 26, there is an incomplete sentence: "As such, the majority of the treatment effectiveness assumptions [new paragraph] Furthermore, patients spend the majority…"	The rest of the sentence "As such, the majority of the treatment effectiveness assumptions" to be provided	It is unclear what the EAG means	Thank you for highlighting this error. The EAG report has been updated as follows, "As such, the majority of the modelled treatment effectiveness in the model is based on assumptions".
Page 71, Table 32, footnotes	Please revisit table footnotes and amend as necessary	Footnote definitions missing/incorrect	Thank you for highlighting this error. The EAG report has been updated to [redacted]

Issue 3 Spelling or grammatical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 22, 77, 91: "[redacted]"	[redacted]	Typographical error	Thank you for highlighting this error. The EAG report has been corrected.
Page 26: "In the NICE manual, it state '*a time horizon…'*…"	"In the NICE manual, it state**s** '*a time horizon…'*…"	Typographical error	Thank you for highlighting this error.

			The EAG report has been corrected.
Page 29: “Additionally, in the EAG scenario, additionally monitoring costs are removed…”	“Additionally, in the EAG scenario, **additional** monitoring costs are removed…”	Typographical error	Thank you for highlighting this error. The EAG report has been corrected.
Page 30: “The results of the ITC demonstrated that both oral antimuscarinics and botulinum toxin A are [redacted]”	“The results of the ITC demonstrated that both oral antimuscarinics and botulinum toxin A are [redacted]”	Typographical error	Thank you for highlighting this error. The EAG report has been corrected.
Page 31: “Using the corrected company base case, the ICER changed from [redacted] to [redacted]…”	“Using the corrected company base case, the ICER changed from [redacted] to [redacted]…”	Typographical error	Thank you for highlighting this error. The EAG report has been corrected.
Page 36: “As a result of the correctios, the ICER for GPB 1% cream versus oral antimuscarinics…”	“As a result of the correctio**n**s, the ICER for GPB 1% cream versus oral antimuscarinics…”	Typographical error	Thank you for highlighting this error. The EAG report has been corrected.
Global: “botox”	“**B**otox”	Typographical error	Thank you for highlighting this error. The EAG report has been corrected.

Page 91: "… [redacted] "	"… [redacted] "	Typographical error	This broken link has not been found in the EAG's report.
Page 71, Table 32, abbreviation list: " [redacted]	[redacted]	Typographical error (Duplication of N = number of patients; NA and NR not defined in the abbreviation list)	Thank you for highlighting this error. The EAG report has been corrected.
Page 100: "…and explored a time horizon of 72 weeks in a scenario analysis (Section 0)."	"…and explored a time horizon of 72 weeks in a scenario analysis (Section **4.2.3**)." Please fix the cross-reference, the Company believes this should be Section **4.2.3**	Broken hyperlink	Thank you for highlighting this error. The EAG report has been corrected.
Page 103: "…to estimate equivalent data for the comparators (**Error! Reference source not found.**), which were then used to estimate transition probabilities in the model (presented in Appendix 0)."	"…to estimate equivalent data for the comparators ([insert correct hyperlink]), which were then used to estimate transition probabilities in the model (presented in Appendix **7.3**)." Please fix the cross-reference, the Company believes this should be Appendix **7.3**	Broken hyperlink	This broken link has not been found in the EAG's report. The cross reference to the appendix has been corrected.
Page 105: "The EAG was concerned with the company's assumption that the proportion	"The EAG was concerned with the company's assumption that the proportion**al** difference between the ORs for the ≥2 point…"	Typographical error	Thank you for highlighting this error. The EAG report has been corrected.

difference between the ORs for the ≥2 point…"			
Page 122: "In the company's economic model, only the costs of subsequent treatment was included…"	"In the company's economic model, only the costs of subsequent treatment **were** included…"	Typographical error	Thank you for highlighting this error. The EAG report has been corrected.
Page 124: "Patients on for GPB 1% cream move to subsequent treatment after [redacted] years and…"	Patients on GPB 1% cream move to subsequent treatment after [redacted] years and…" (delete the word "for")	Typographical error	Thank you for highlighting this error. The EAG report has been corrected.
Page 126: "…of subsequent treatments dependent on initial treatment (**Error! Reference source not found.**,and…"	"…of subsequent treatments dependent on initial treatment ([insert correct hyperlink]**)**,and..." (missing close bracket)	Typographical error	This broken link has not been found in the EAG's report.
Page 167: "…using EQ-5D-5L utilities (which NICE isn't recommended by NICE)."	"…using EQ-5D-5L utilities (which isn't recommended by NICE)." (delete the first "NICE")	Typographical error	Thank you for highlighting this error. The EAG report has been corrected.

Issue 4 Confidential markup

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 25	"…the ICER [redacted] from [redacted] to [redacted] for the comparison with propantheline bromide…"	"…the ICER [redacted] from [redacted] to [redacted] for the comparison with propantheline bromide…" Please redact the direction of the ICER	The EAG report has been amended.
Page 60, 90	"…but notes that the company considers the full effect of the cream would be visible after 4 weeks (week 8 for placebo patients from 3a entering 3b, [redacted] …"	"…but notes that the company considers the full effect of the cream would be visible after 4 weeks (week 8 for placebo patients from 3a entering 3b, [redacted]…" Please redact to align with other redacted text in the report	The EAG report has been amended.
Page 65	[redacted]	[redacted] Please redact to align with other redacted text in the report	The EAG report has been amended.
Page 68	[redacted]whereas the company's primary proposed positioning of GPB 1% cream is following lifestyle advice and topical 20% aluminium chloride hexahydrate preparations, such as roll-on antiperspirants and sprays."	[redacted]whereas the company's primary proposed positioning of GPB 1% cream is following lifestyle advice and topical 20% aluminium chloride hexahydrate preparations, such as roll-on antiperspirants and sprays." [redacted]Please redact to align with other redacted text in the report	The EAG report has been amended.

Page 72	"…[redacted], the absolute reduction in sweat production from baseline to Week 12 for Phase 3b FASnewb in…"	"…In addition, the absolute reduction in sweat production from baseline to Week 12 for Phase 3b FASnewb in…" Please remove CI marking as this redaction is not needed	The EAG report has been amended.
Page 74, 89	Page 74, Page 89:[redacted] Page 74, Table 33, final row: "HDSS response [redacted]"	"The HDSS response rate at day 29 in Phase 3a was numerically higher with GPB 1% cream (23.0%) compared with placebo (11.9%) but the difference between groups was not statistically significant (p = 0.054 [Table 33])." "HDSS response 20 (23.0) 10 (11.9) 0.44 (0.19 to 1.03) 0.0542" Please remove CI marking as this redaction is not needed	The EAG report has been amended.
Page 75	"…at baseline (r=[redacted]), week 4 (r=[redacted]), and week 12 (r=[redacted]), [redacted]	"…at baseline (r=[redacted]), week 4 (r=[redacted]), and week 12 (r=[redacted]), [redacted]." Please redact the direction of the relationship	The EAG report has been amended.
Page 76	"In Phase 3a, [redacted]GPB 1% cream [redacted] compared with placebo [redacted]"	"In Phase 3a[redacted]GPB 1% cream [redacted] compared with placebo [redacted]" Please redact as this information was redacted in Table 40 of the company's CQ response	The EAG report has been amended.
Page 79	"In fact, AEs for [redacted]based on the following statements:"	"In fact, AEs for [redacted]based on the following statements:" Please redact to align with other redacted text in the	The EAG report has been amended.

		report	
Page 81	"…while there may be some differences between treatments in terms of the profile of AEs that may be experienced, [redacted] that will likely not receive a specific treatment, with dose interruptions…" "Based on the feedback received from the clinical expert and the statement within the CSR for the Hyp1-18/2016 trial that [redacted], the EAG requested…"	"…while there may be some differences between treatments in terms of the profile of AEs that may be experienced, [redacted] that will likely not receive a specific treatment, with dose interruptions…" "Based on the feedback received from the clinical expert and the statement within the CSR for the Hyp1-18/2016 trial that [redacted], the EAG requested…" Please redact to align with other redactions in the report	The EAG report has been amended.
Page 91	"…may be experienced, [redacted] that will likely not…" "However, based on feedback received from the EAG's clinical expert and the statement within the [redacted], the EAG…"	"…may be experienced, [redacted] that will likely not…" "However, based on feedback received from the EAG's clinical expert and the statement within the [redacted], the EAG…" Please redact to align with other redactions in the report	The EAG report has been amended.

Page 112	"However, none of the studies used to obtain adverse events, including the key trial, [redacted] with inconsistent definitions used across studies."	"However, none of the studies used to obtain adverse events, including the key trial, [redacted] with inconsistent definitions used across studies." Please redact to align with other redactions in the report	The EAG report has been amended.
Page 120	"…based on the EAG's preferred approach and while the ICER remained dominant, the estimated QALY gain [redacted] to [redacted]."	"…based on the EAG's preferred approach and while the ICER remained dominant, the estimated QALY gain [redacted] to [redacted]." Please redact the direction of the ICER	The EAG report has been amended.
Page 121	"The cost of non-axillary hyperhidrosis is based on the company's modelling of oral antimuscarinics in the model. In the model, [redacted] non-…"	"The cost of non-axillary hyperhidrosis is based on the company's modelling of oral antimuscarinics in the model. In the model, [redacted] non-…" Please redact to align with other redactions in the report	The EAG report has been amended.
Page 125	"… have a substantial impact on the estimated QALY gain, [redacted] to [redacted] for the comparison…"	"… have a substantial impact on the estimated QALY gain, [redacted] to [redacted] for the comparison…" Please redact the direction of the ICER	The EAG report has been amended.
Page 144	Table 65, Column 4, Row 2, Exploratory analysis number 1: "[redacted]"	"[redacted]" Please redact to align with other redactions in the report	The EAG report has been amended.
Page 149	Table 67, Column 8, Row 10, Scenario 6 + two-year time horizon: "[redacted]"	"Dominant" Please remove CI marking as this redaction is not	The EAG report has been amended.

		needed	
Page 182	Table 86, Column 2–4, Row 3, Company corrected base case: “[redacted]”	“[redacted]” Please redact to align with other redacted text in the report	The EAG report has been amended.
Page 184	Table 87, Column 7, Row 24, B22bi: “[redacted]”	“Dominant” Please removed CI marking as this redaction nis not needed	The EAG report has been amended.

Updated Company base case

Table 2 outlines the stepwise changes made from the revised company base case submitted in response to the Clarification Questions to the updated base case comparisons of GPB 1% cream versus oral antimuscarinics and versus botulinum toxin A. These changes reflect updates to the cost of propantheline bromide based on the most recent prescribing data i.e., reinstatement of the higher price (£103.52) in line with current clinical practice. The updated base case and corresponding revised sensitivity analyses are presented below.

Table 2: Step changes from revised Company base case to updated Company base case

	vs. Antimuscarinics		vs. Botulinum toxin	
	ICER	**NMB**	**ICER**	**NMB**
Revised Company base case (as presented in response to the Clarification Questions)	Dominant	[redacted]	Dominant	[redacted]
Updated Company base case (reflecting a cost of £103.52 for propantheline bromide)	**Dominant**	[redacted]	**Dominant**	[redacted]

Abbreviations: CQ, clarification question; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit

Updated base-case results

Table 3 presents the updated base case pairwise results vs. GPB 1% cream and Table 4 presents the corresponding updated net health benefits (NHBs) vs. GPB 1% cream.

GPB 1% cream vs. antimuscarinics

In the updated base case analysis, GPB 1% cream generates [redacted] additional QALYs at a reduced cost of [redacted] compared to antimuscarinics. As it delivers greater health benefits at a lower overall cost, GPB 1% cream is considered dominant relative to antimuscarinics. The NHB is [redacted] at a WTP threshold of £20,000, and [redacted] at a threshold of £30,000. Corresponding NMBs are [redacted] and [redacted], respectively.

GPB 1% cream vs. botulinum toxin

In the updated base case analysis, GPB 1% cream generates [redacted] additional QALYs at a reduced cost of [redacted] compared to botulinum toxin. As it delivers greater health benefits at a lower overall cost, GPB 1% cream is considered dominant relative to botulinum toxin. The NHB is [redacted] at a WTP threshold of £20,000, and [redacted] at a threshold of £30,000. Corresponding NMBs are [redacted] and [redacted], respectively.

Table 3: Updated base-case results vs. GPB 1% cream

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
GPB 1% cream	[redacted]	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: GPB, glycopyrronium bromide; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 4: Updated net health benefit vs. GPB 1% cream

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
GPB 1% cream	[redacted]	[redacted]				
Antimuscarinics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

Updated sensitivity analyses

Probabilistic sensitivity analysis

The proportion of PSA iterations where GPB 1% cream is considered cost-effective is [redacted] at a £20,000/QALY threshold. The CEAC is shown in Figure 1. The convergence plots for the PSA for vs. antimuscarinics and vs. botulinum toxin are presented in Figure 2 and Figure 3, respectively, based on the NMB endpoint.

Figure 1: Updated CEAC

Abbreviations: CEAC, cost-effectiveness acceptability curve; GPB, glycopyrronium bromide.

Figure 2: PSA convergence plot for GPB 1% cream vs. antimuscarinics

Abbreviations: GPB, glycopyrronium bromide; NMB, net monetary benefit; PSA, probabilistic sensitivity analysis

Figure 3: PSA convergence plot for GPB 1% cream vs. botulinum toxin

Abbreviations: GPB, glycopyrronium bromide; NMB, net monetary benefit; PSA, probabilistic sensitivity analysis

The PSA results indicate an average incremental cost of [redacted] and an average incremental QALY gain of [redacted] for GPB 1% cream compared to antimuscarinics. These results are consistent with the deterministic analysis, confirming that GPB 1% cream is dominant (i.e., more effective and less costly). This consistency is visually supported by the overlap of the deterministic and probabilistic base case markers in the cost-effectiveness plane (Figure 4).

Figure 4: Updated cost-effectiveness plane (1,000 iterations) | GPB 1% cream vs. antimuscarinics

Abbreviations: GPB, glycopyrronium bromide; QALY, quality adjusted life year; WTP, willingness-to-pay.

For the comparison with botulinum toxin, the PSA shows an average incremental cost of [redacted] and an average incremental QALY gain of [redacted] for GPB 1% cream. Again, the probabilistic results are aligned with the deterministic findings, indicating dominance of GPB 1% cream. This is further evidenced by the overlap in the deterministic and probabilistic results on the cost-effectiveness plane (Figure 5).

Figure 5: Updated cost-effectiveness plane (1,000 iterations) | GPB 1% cream vs. botulinum toxin

Abbreviations: GPB, glycopyrronium bromide; QALY, quality adjusted life year; WTP, willingness-to-pay.

Deterministic sensitivity analysis

Results for the ten most influential parameters for GPB 1% cream vs. antimuscarinics are shown in Table 5 and depicted in a tornado diagram in Figure 6 and Figure 7 based on the ICER and a NMB with a WTP of £20,000, respectively.

Table 5: Top ten parameters impacting the ICER (updated one-way sensitivity analysis) | GPB 1% cream vs. antimuscarinics

Parameter	Lower bound	Upper bound	Difference
Utilities HDSS=4	[redacted]	[redacted]	[redacted]
Utilities HDSS=3	[redacted]	[redacted]	[redacted]
Antimuscarinics: 2-week proportion of AEs, Non-axillary sweating/hyperhidrosis	[redacted]	[redacted]	[redacted]

Parameter	Lower bound	Upper bound	Difference
Utilities HDSS=2	[redacted]	[redacted]	[redacted]
Antimuscarinics: Proportion of discontinuations 0-26 weeks	[redacted]	[redacted]	[redacted]
GPB 1% cream: Proportion of discontinuations 0-72 weeks	[redacted]	[redacted]	[redacted]
Antimuscarinics: proportion Unlicensed GPB (secondary care)	[redacted]	[redacted]	[redacted]
Antimuscarinics: proportion Botulinum toxin (secondary care) subsequent therapy	[redacted]	[redacted]	[redacted]
GPB 1% cream: proportion Botulinum toxin (secondary care) subsequent therapy	[redacted]	[redacted]	[redacted]
Propantheline bromide: cost per pack	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; ICER, incremental cost-effectiveness ratio.

Figure 6: Tornado plot, ICER (updated one-way sensitivity analysis) | GPB 1% cream vs. antimuscarinics

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; ICER, incremental cost-effectiveness ratio.

Figure 7: Tornado plot, NMB at a WTP of £20,000 (updated one-way sensitivity analysis) | GPB 1% cream vs. antimuscarinics

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; NMB, net monetary benefit; WTP, willingness-to-pay.

Results for the ten most influential parameters for GPB 1% cream vs. botulinum toxin are shown in Table 6 and depicted in a tornado diagram in Figure 8 and Figure 9 based on the ICER and a NMB with a WTP of £20,000, respectively.

Table 6: Top ten parameters impacting the ICER (updated one-way sensitivity analysis) | GPB 1% cream vs. botulinum toxin

Parameter	Lower bound	Upper bound	Difference
Utilities HDSS=4	[redacted]	[redacted]	[redacted]
Utilities HDSS=3	[redacted]	[redacted]	[redacted]
Utilities HDSS=2	[redacted]	[redacted]	[redacted]
Subsequent therapy costs: unlicensed GPB (secondary care)	[redacted]	[redacted]	[redacted]
Botulinum toxin: proportion unlicensed GPB (secondary care) subsequent therapy	[redacted]	[redacted]	[redacted]
Botulinum toxin: Proportion of discontinuations 0-26 weeks	[redacted]	[redacted]	[redacted]
Utilities HDSS=1	[redacted]	[redacted]	[redacted]
Subsequent therapy costs: Botulinum toxin (secondary care)	[redacted]	[redacted]	[redacted]
Unlicensed GPB: cost per tube	[redacted]	[redacted]	[redacted]
Number of Botulinum toxin procedures per year	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; ICER, incremental cost-effectiveness ratio.

Figure 8: Tornado plot, ICER (updated one-way sensitivity analysis) | GPB 1% cream vs. botulinum toxin

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; ICER, incremental cost-effectiveness ratio.

Figure 9: Tornado plot, NMB at a WTP of £20,000 (updated one-way sensitivity analysis) | GPB 1% cream vs. botulinum toxin

Abbreviations: FAS, full analysis set; GPB, glycopyrronium bromide; HDSS, Hyperhidrosis Disease Severity Score; NMB, net monetary benefit; WTP, willingness-to-pay.

Scenario analysis

Scenario analyses were conducted to assess structural uncertainty within the economic model. The corresponding results from the deterministic analyses for GPB 1% cream vs. antimuscarinics are shown in Table 7 and Table 8 for the ICER and NMB with a WTP of £20,000, respectively. For GPB 1% cream vs. botulinum toxin these are shown in Table 9 and Table 10, respectively.

Across all scenarios, GPB 1% cream remains cost-effective i.e., the NMB remains positive at a WTP threshold of £20,000.

Table 7: Updated deterministic scenario analyses (ICER) | GPB 1% cream vs. antimuscarinics

Scenario name	ICER	% change from base case
Base case	[redacted]	NA
Time horizon: 4-years	[redacted]	386.3%
Time horizon: 5-years	[redacted]	245.3%
Time horizon: 10-years	[redacted]	42.8%
Half cycle correction: excluded	[redacted]	7.3%
Discount rate: 0% costs and 0% outcomes	[redacted]	-67.0%
Baseline characteristics: FASa	[redacted]	1.3%
Baseline characteristics: PPSb	[redacted]	0.6%
Baseline GPB 1% cream efficacy: PPSb	[redacted]	-23.3%
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	-23.1%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on PPSa	[redacted]	-1.1%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on Wade et al. (2017)	[redacted]	-0.9%

Scenario name	ICER	% change from base case
Relative efficacy of GPB 1% cream vs. botulinum toxin based on PPSa	[redacted]	0.0%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on Wade et al. (2017)	[redacted]	0.0%
Relative efficacy of GPB 1% cream vs. botulinum toxin ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	0.0%
Dose of botulinum toxin assumed 150U	[redacted]	1.9%
Dose of botulinum toxin assumed combined of 100U and 150U	[redacted]	0.9%
Relative efficacy for 2+ botulinum toxin procedures based on Lowe et al. (2007)	[redacted]	0.0%
Relative efficacy for 2+ botulinum toxin procedures based on a 10% reduction in OR	[redacted]	0.0%
Relative efficacy for 2+ botulinum toxin procedures based on a 20% reduction in OR	[redacted]	0.0%
Maximum botulinum toxin efficacy achieved at week 8	[redacted]	0.0%
Maximum botulinum toxin efficacy achieved at week 12	[redacted]	0.0%
1.8 botulinum procedures per year	[redacted]	0.2%
Cost of propantheline bromide of £20.74	[redacted]	-80.5%
Dose per day of oxybutynin of 12.5mg	[redacted]	0.9%
Dose intensity for oral antimuscarinics assumed equal to GPB 1% cream	[redacted]	-43.2%

Scenario name	ICER	% change from base case
Increase in discontinuation rate with GPB 1% cream of 10%	[redacted]	17.8%
Increase in discontinuation rate with GPB 1% cream of 20%	[redacted]	34.7%
Source of discontinuation for antimuscarinics from Millan-Cayetano et al. (2017)	[redacted]	5578.1%
Discontinuation for botulinum toxin assumed as only those who were formally discontinued	[redacted]	10.3%
Discontinuation for botulinum toxin assumed as those who were formally discontinued and no further treatment	[redacted]	-2.0%

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; GPB, glycopyrronium bromide; NMB, net monetary benefit; PPS, per-protocol set; WTP, willingness-to-pay.

Table 8: Updated deterministic scenario analyses (NMB based on a £20,000 WTP) | GPB 1% cream vs. antimuscarinics

Scenario name	NMB	% change from base case
Base case	[redacted]	NA
Time horizon: 4-years	[redacted]	-18.9%
Time horizon: 5-years	[redacted]	-14.1%
Time horizon: 10-years	[redacted]	-3.4%
Half cycle correction: excluded	[redacted]	0.8%
Discount rate: 0% costs and 0% outcomes	[redacted]	6.8%
Baseline characteristics: FASa	[redacted]	-0.8%
Baseline characteristics: PPSb	[redacted]	-0.3%

Scenario name	NMB	% change from base case
Baseline GPB 1% cream efficacy: PPSb	[redacted]	26.8%
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	26.4%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on PPSa	[redacted]	1.0%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on Wade et al. (2017)	[redacted]	0.8%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on PPSa	[redacted]	0.0%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on Wade et al. (2017)	[redacted]	0.0%
Relative efficacy of GPB 1% cream vs. botulinum toxin ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	0.0%
Dose of botulinum toxin assumed 150U	[redacted]	0.2%
Dose of botulinum toxin assumed combined of 100U and 150U	[redacted]	0.1%
Relative efficacy for 2+ botulinum toxin procedures based on Lowe et al. (2007)	[redacted]	0.0%
Relative efficacy for 2+ botulinum toxin procedures based on a 10% reduction in OR	[redacted]	0.0%
Relative efficacy for 2+ botulinum toxin procedures based on a 20% reduction in OR	[redacted]	0.0%
Maximum botulinum toxin efficacy achieved at week 8	[redacted]	0.0%

Scenario name	NMB	% change from base case
Maximum botulinum toxin efficacy achieved at week 12	[redacted]	0.0%
1.8 botulinum procedures per year	[redacted]	0.0%
Cost of propantheline bromide of £20.74	[redacted]	-9.6%
Dose per day of oxybutynin of 12.5mg	[redacted]	0.1%
Dose intensity for oral antimuscarinics assumed equal to GPB 1% cream	[redacted]	-5.1%
Increase in discontinuation rate with GPB 1% cream of 10%	[redacted]	-6.1%
Increase in discontinuation rate with GPB 1% cream of 20%	[redacted]	-11.1%
Source of discontinuation for antimuscarinics from Millan-Cayetano et al. (2017)	[redacted]	-9.9%
Discontinuation for botulinum toxin assumed as only those who were formally discontinued	[redacted]	1.2%
Discontinuation for botulinum toxin assumed as those who were formally discontinued and no further treatment	[redacted]	-0.2%

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; GPB, glycopyrronium bromide; NMB, net monetary benefit; PPS, per-protocol set; WTP, willingness-to-pay.

Table 9: Updated deterministic scenario analyses (ICER) | GPB 1% cream vs. botulinum toxin

Scenario name	ICER	% change from base case
Base case	[redacted]	NA
Time horizon: 4-years	[redacted]	88.1%

Scenario name	ICER	% change from base case
Time horizon: 5-years	[redacted]	59.6%
Time horizon: 10-years	[redacted]	10.6%
Half cycle correction: excluded	[redacted]	1.3%
Discount rate: 0% costs and 0% outcomes	[redacted]	-22.4%
Baseline characteristics: FASa	[redacted]	1.0%
Baseline characteristics: PPSb	[redacted]	0.4%
Baseline GPB 1% cream efficacy: PPSb	[redacted]	-31.7%
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	-22.1%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on PPSa	[redacted]	1.5%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on Wade et al. (2017)	[redacted]	4.6%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on PPSa	[redacted]	-2.7%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on Wade et al. (2017)	[redacted]	0.3%
Relative efficacy of GPB 1% cream vs. botulinum toxin ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	4.6%
Dose of botulinum toxin assumed 150U	[redacted]	1.8%
Dose of botulinum toxin assumed combined of 100U and 150U	[redacted]	0.9%

Scenario name	ICER	% change from base case
Relative efficacy for 2+ botulinum toxin procedures based on Lowe et al. (2007)	[redacted]	4.7%
Relative efficacy for 2+ botulinum toxin procedures based on a 10% reduction in OR	[redacted]	-0.9%
Relative efficacy for 2+ botulinum toxin procedures based on a 20% reduction in OR	[redacted]	-1.8%
Maximum botulinum toxin efficacy achieved at week 8	[redacted]	8.6%
Maximum botulinum toxin efficacy achieved at week 12	[redacted]	15.5%
1.8 botulinum procedures per year	[redacted]	4.6%
Cost of propantheline bromide of £20.74	[redacted]	-8.3%
Dose per day of oxybutynin of 12.5mg	[redacted]	0.1%
Dose intensity for oral antimuscarinics assumed equal to GPB 1% cream	[redacted]	-4.5%
Increase in discontinuation rate with GPB 1% cream of 10%	[redacted]	5.4%
Increase in discontinuation rate with GPB 1% cream of 20%	[redacted]	10.6%
Source of discontinuation for antimuscarinics from Millan-Cayetano et al. (2017)	[redacted]	58.9%
Discontinuation for botulinum toxin assumed as only those who were formally discontinued	[redacted]	391.6%
Discontinuation for botulinum toxin assumed as those who were formally discontinued and no further treatment	[redacted]	-34.4%

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; GPB, glycopyrronium bromide; NMB, net monetary benefit; PPS, per-protocol set; WTP, willingness-to-pay.

Table 10: Updated deterministic scenario analyses (NMB) | GPB 1% cream vs. botulinum toxin

Scenario name	NMB	% change from base case
Base case	[redacted]	NA
Time horizon: 4-years	[redacted]	-23.4%
Time horizon: 5-years	[redacted]	-17.4%
Time horizon: 10-years	[redacted]	-4.4%
Half cycle correction: excluded	[redacted]	0.4%
Discount rate: 0% costs and 0% outcomes	[redacted]	6.1%
Baseline characteristics: FASa	[redacted]	-0.7%
Baseline characteristics: PPSb	[redacted]	-0.3%
Baseline GPB 1% cream efficacy: PPSb	[redacted]	30.8%
Patients remaining on treatment with GPB 1% cream beyond 72 weeks continue to improve outcomes	[redacted]	18.9%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on PPSa	[redacted]	-1.0%
Relative efficacy of GPB 1% cream vs. antimuscarinics based on Wade et al. (2017)	[redacted]	-2.9%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on PPSa	[redacted]	1.8%
Relative efficacy of GPB 1% cream vs. botulinum toxin based on Wade et al. (2017)	[redacted]	-0.2%

Scenario name	NMB	% change from base case
Relative efficacy of GPB 1% cream vs. botulinum toxin ≥1 HDSS score assumed the same as ≥2 HDSS score	[redacted]	-2.9%
Dose of botulinum toxin assumed 150U	[redacted]	1.0%
Dose of botulinum toxin assumed combined of 100U and 150U	[redacted]	0.5%
Relative efficacy for 2+ botulinum toxin procedures based on Lowe et al. (2007)	[redacted]	-3.0%
Relative efficacy for 2+ botulinum toxin procedures based on a 10% reduction in OR	[redacted]	0.6%
Relative efficacy for 2+ botulinum toxin procedures based on a 20% reduction in OR	[redacted]	1.2%
Maximum botulinum toxin efficacy achieved at week 8	[redacted]	-5.2%
Maximum botulinum toxin efficacy achieved at week 12	[redacted]	-8.9%
1.8 botulinum procedures per year	[redacted]	-1.5%
Cost of propantheline bromide of £20.74	[redacted]	-2.8%
Dose per day of oxybutynin of 12.5mg	[redacted]	0.0%
Dose intensity for oral antimuscarinics assumed equal to GPB 1% cream	[redacted]	-1.5%
Increase in discontinuation rate with GPB 1% cream of 10%	[redacted]	-6.0%
Increase in discontinuation rate with GPB 1% cream of 20%	[redacted]	-10.7%

Scenario name	NMB	% change from base case
Source of discontinuation for antimuscarinics from Millan-Cayetano et al. (2017)	[redacted]	19.8%
Discontinuation for botulinum toxin assumed as only those who were formally discontinued	[redacted]	-12.6%
Discontinuation for botulinum toxin assumed as those who were formally discontinued and no further treatment	[redacted]	1.0%

Abbreviations: FAS, full analysis set; HDSS, Hyperhidrosis Disease Severity Score; GPB, glycopyrronium bromide; NMB, net monetary benefit; PPS, per-protocol set; WTP, willingness-to-pay.