LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Glycopyrronium Cantabria (glycopyrronium bromide)

SE/H/2170/01/DC

This module reflects the scientific discussion for the approval of Glycopyrronium Cantabria. The procedure was finalised on 2022-07-13. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Glycopyrronium Cantabria, 2,2 mg/ actuation, Cream.

The active substance is glycopyrronium bromide. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Glycopyrronium Cantabria, 2,2 mg/ actuation, Cream, is submitted according to Article 8(3) of Directive 2001/83/EC. The applicant, Industrial Farmaceutica Cantabria S.A. applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and ES, IT and PT as concerned member states (CMS).

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

Paediatric Regulation

The applicant has obtained a partial PIP waiver from the PDCO/EMA for some subsets of the paediatric population for Glycopyrronium Cantabria.
In accordance with article 7 of Regulation 1901/2006, as amended, the applicant has submitted a paediatric investigation plan EMEA-002383-PIP0l-18. The European Medicines Agency's decision P/0420/2020 was provided on 23rd of October 2020. The European Medicines Agency has deferred the obligation to submit the results of studies with Glycopyrronium Cantabria. Furthermore, the agreed Paediatric Investigation Plan is not fully completed yet as only some of the measures are completed

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology

Hyperhidrosis results from overstimulation of the eccrine sweat glands, most often those located in the axillae. 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, GP inhibits ACh-driven sympathetic actions on various exocrine glands, including sweat glands. The Applicant has provided with literature data showing that GPB is a competitive inhibitor of the mAChRs. The substance has a high binding affinity to all five muscarinic mAChR subtypes and *in vitro* inhibitory dissociation constants (Ki) in the lower nanomolar range for human isoforms of the mAChR subtypes. The Applicant has also submitted a study evaluating GPB binding to the five recombinant mACh receptor subtypes expressed on CHO-K1 cells. However, the study submitted is not well described in the study report, and the experimental set-up is overall unclear. Given that the overview documents lacks further clarity on these matters, the Applicant is asked to clarify this. In the response, the Applicant agreed that the experimental set-up for the Eurofins study was unclear and provided with Annexes where aspects of the general methodology is described. While the lack of further information rendered it impossible to fully assess the relevance of the study data, the results provided are in line with data from studies in the publication domain evaluating the issue (i.e. Gavaldà et al. (https://doi.org/10.1016/j.pupt.2014.05.005)). Therefore, the issue was not further pursued. Based on the results, GPB had the highest binding affinity for the M1- receptor (IC50=1.53 nM) followed by the M4 (IC50=1.89 nM), M5 (IC50=2.11 nM), M3 (IC50=2.71 nM), and M2 (IC50=3.29 nM) suggesting that the affinities for all five receptors are in the low nanomolar range.
One secondary pharmacodynamics study has been referenced by the Applicant, which showed that GPB had no effect on neurokinin-A-induced contraction of isolated tracheal smooth muscle. While of limited relevance for the present Application, the overall impression is that the lengthy clinical experience of GP limits the usefulness of further secondary pharmacodynamics studies.

No safety pharmacology studies have been performed with Glycopyrronium Cantabria. The Applicant has referenced the safety pharmacology studies for GPB in the Seebri Breezhaler EPAR. hERG inhibition was noted only at GPB concentrations sufficiently above MHRD. However, in beagle dogs, transient effects were noted on heart rate, blood pressure and QT-interval. Further, in the 4-week study, tachycardia was a frequent finding at doses ≥0.077 mg/kg/day. Potential cardiovascular effects of GPB are clinically recognized according to the Seebri SmPC.
Passage of GPB to CNS is considered limited, and given the low systemic exposure of GP after dermal exposure CNS effects are not likely. Likewise, since there is only low systemic exposure following topical application of GPB 10 mg/g cream, an impact on the resopiratory system is not likely. Further, the safety pharmacology studies for the inhaled Seebri breezhaler did not reveal any treatment-related effects on the respiratory system in rats at an inhaled dose of 0.168 mg/kg GPB. Collectively, while cardiovascular effects have been shown for another GPB product, the limited systemic exposure after dermal use of Glycopyrronium Cantabria is unlikely to result in effects on safety pharmacology parameters in the clinical setting.

No pharmacodynamic drug interaction studies have been performed. However, in line with SmPC documents of previously approved GP products, an interaction with other anticholinergic medical drugs is possible.

Collectively, the pharmacology studies presented and referenced are considered sufficient to support the present Application for Glycopyrronium Cantabria.

Pharmacokinetics

The Applicant has not performed any pharmacokinetics studies with Glycopyrronium Cantabria to support the present Application. Referenced data from EPARs of previously approved products have been included. However, the Applicant presented a validation report he LC-MS/MS method developed for determination of GP concentrations in minpig plasma and buffer which was considered adequate for the purpose.

The Applicant has provided with absorption study data for previously approved (EU or US) products. No separate pharmacokinetic studies of absorption have been performed with Glycopyrronium Cantabria. However, the toxicokinetics from the 7-day repeated dose study in minipigs where 0.5% to 2% GPB in cream was used (see toxicology section) revealed that Cmax and AUClast values increased with increasing dose in a largely dose-dependent manner on Days 1 and 7. Further, the Cmax and AUClast noted on Day 7 following topical daily treatment with GPB 10 mg/g cream were Cmax = 56.6 pg/mL and AUClast = 569 h*pg/mL. Collectively the data show that low systemic GP exposures are expected after dermal Glycopyrronium Cantabria administration.

Referenced studies from previously approved GP products show that 14C-labeled GPB was taken up and retained in melanin-containing structures following oral or intravenous administration. Further, in the mouse, peak 14C-labeled GPB radioactivity was found in all organs at 5-10 minutes except brain whereas liver, kidney and intestines showed traces of activity at 24 hours. Of relevance for reproductive toxicity, no or limited placenta transfer was observed in pregnant mice, rabbits, dogs and humans but GP and its metabolites distributed to milk and reached a milk-plasma ratio of 11. Referenced studies on metabolism of GPB from public literature and public assessment reports show that GPB is mainly metabolized via cytochrome P450 (CYP)–mediated oxidative metabolism. No unique human metabolites were identified in liver microsomes and hepatocytes. It is also noted that the expression of CYP enzymes seem to be at least 300-fold lower in skin microsomal fraction compared to liver microsomal fraction.

Excretion of GP is dependent on the route of administration. Studies using i.v. administration have shown that excretion was mainly via urine (60%) and bile/faeces (40%), wheres p.o. administration of GP was mainly excreted via faeces (>90%), suggesting that the swallowed dose is not absorbed. No data on excretion after dermal administration is available. However, while low systemic concentrations are expected after dermal administration, it is assumed that faeces and urine represent major excretion pathways.

Toxicology

In support of the present application, the applicant is referring to both published data and original non-clinical studies. The toxicity of GP-containing products has been characterized in various non-clinical programs supporting approval of GP-containing products (Seebri, Cuvposa and Qbrexza). In addition, the applicant has performed new studies for this application which included a 7-day dermal local tolerance study in minipig, QSAR analyses of impurities, In Vitro Bovine Corneal Opacity and Permeability Test, In Vitro EpiOcular and an In Vivo Local Lymph Node Assay. The clinical formulation was used in the studies.

No single-dose studies have been performed by the applicant, and they are not considered warranted. However, the Applicant has referenced LD50-data from previous GP products. While these studies are old, it is stressed that LD50-data is of limited regulatory relevance.

The applicant refers to several published repeat-dose toxicity studies for other GP-containing products (oral, inhalative and topical) that supported marketing approvals. Studies were performed in rats, dogs,

mice and minipigs. GP-induced toxicities were mainly related to the pharmacology of the substance as a mACh antagonist with effects such as mydriasis, reduced excretion from exocrine glands and tachycardia. Hence, dry oral mucosa or gums, reduced lacrimal gland secretions, hypertrophy of the salivary or lacrimal glands and mild inflammation, dilation of the ducts and/or alveoli of the sub mucosal glands in the pharynx were observed. Further, effects were noted on body weight. Reduced food intake and reduced body weight gain were observed in rats while reduced food intake was seen in dogs when treated by inhalation. Repeat-dose studies in mice and rats with oral administration of GPB revealed a reduction in mean weight gain for both species. Survival was reduced in a 13-week repeated dose studies in mice, this was not seen in any other species. The causes of the treatment-related mortality and reduced body weight gain were unclear. Regarding studies with dermal application, rats treated with 20% solution showed induced excessive local irritation at the treatment site, resulting in premature sacrifice or cessation of dosing of several animals. Reduced mean body weight and mean body weight change (gain) were observed in groups treated with ≥6% solution in male rats but not in female. In a 39-week study in minipigs, no adverse toxicities were noted despite exposures up to 44mg/kg daily. Collectively, GPB is well-tolerated with mainly pharmacology-related toxicities.

Published literature from other GP-containing drug products that supported marketing approval of oral, inhalative and topical drug products have not shown any genotoxicity.

Other approved GP-containing products have not presented any carcinogenic effects; hence, no carcinogenic risk is expected for topical use. The Applicant’s justification for not having conducted carcinogenicity studies is acceptable.

Reproductive and developmental toxicity of GPB has been studied in already approved GPB-containing products. Subcutaneous and inhalation routs of administration of GPB revealed no effects on male rat fertility parameters (including sperm counts and sperm motility) at 1.5 mg/kg GP. In female rats, decreases in the number of corpora lutea and implantation sites were observed with a NOAEL of 0.5 mg/kg/day GP. No effects on embryo-foetal development were observed in pregnant rats exposed to GPB via inhalation during gestation days 6 to 17 and in pregnant rabbits inhaling GPB during gestation days 7 through 19. Pre- and postnatal development was not affected in a study applying s.c. GPB dosing of pregnant rats. Oral administration of 100 mg/kg/day in a study assessing effects on fertility or general reproductive function in rats revealed no treatment-related effects. Based on the low systemic exposure after dermal application, the risk for foetal exposure and consequently an impact on foetal development is low. The applicant’s justification for not having conducted Reproductive and developmental toxicity studies is acceptable.

The labelling in section 4.6 has been written in accordance with the data presented and the preceived risk. It takes into account the DART data available and the clinical systemic exposure to GPB during Glycopyrronium Cantabria. The contact of the suckling child with the cream or Glycopyrronium Cantabria-treated skin should be avoided. Furthermore, skin to skin contact between treated skin area with other areas including skin of others should be avoided (not only during breast-feeding). Therefore, information regarding the risk associated with any skin to skin contact has been included in 4.4.

Regarding studies in juvenile animals, dermal application with GPB 10 mg/g cream resulted in a much lower systemic exposure compared to treatment with already approved GPB products. The 7-day dermal local tolerance and toxicity study in minipigs (discussed below) showed that all tested concentrations and formulations were well tolerated and there were no adverse findings at the application sites. Further, there is considerable clinical experience from treating juvenile patients with other topical GPB products, why no additional non-clinical studies are considered needed.

The applicant has conducted a 7-Day dermal local tolerance and toxicity study in minipigs to investigate the local and systemic tolerability. The test item was administered daily for 7 consecutive days at local concentrations of 0, 0.5%, 1%, 2% (GPB 10 mg/g cream), and 0, 4% (gel) GPB corresponding to daily doses of 0, 0.11, 0.22, 0.45, 0.89 mg/kg GPB (corresponding to 0.09, 0.18,

0.36, 0.71 mg/kg GP, respectively). Blood was sampled for toxicokinetic evaluation at pretest and Days 1, 3, 5 and 7 and formulations in the syringe were analyzed on Days 1 and 7. The study shows that the GPB cream and gel were well tolerated at all concentrations tested. There were no test item-related mortalities, clinical signs, findings at the application site, changes in body weight, food consumption and clinical laboratory parameters or test item-related pathomorphologic findings. There were no signs of local intolerance at macroscopic or microscopic evaluations. GP was absorbed slowly and to a limited extent, i.e. systemic exposure was low.

The applicant has conducted a local tolerance study to evaluate the eye hazard potential of GBP cream using the bovine corneal opacity and permeability test. GBP cream did not induce ocular irritation through both endpoints (opacity and permeability) and therefore, it was concluded that GPB 10 mg/g cream is not classified as eye irritant.

In addition, the applicant has conducted a local tolerance study to evaluate the eye hazard potential of GBP cream using the Reconstructed Human EpiOcular™ Model. The study concluded that GPB 10 mg/g cream is not classified as eye irritant.

The Local Lymph Node Assay (OECD 429, Study No. 20241154) was designed to evaluate whether the test item induces skin sensitization. The study concluded that GPB cream would be regarded as having potential as very weak skin sensitizer. However, the 7-day dermal local tolerance and toxicity study in minipigs (Study No. 509876) showed that all tested concentrations and formulations were well tolerated after repeated administrations and there were no adverse findings at the application sites. Considering the unclear clinical relevance of the findings, the Applicant has included the information in section 5.3 of the SmPC.

The lack of studies on antigenicity, immunotoxicity, dependence, metabolism and phototoxicity is considered acceptable.

The applicant has provided an *in silico* toxicology analysis with the parent compound GPB and both hydrolysis products ((2RS)-2-cyclopentyl-2-hydroxy-2-phenylacetic acid and (3RS)-3-hydroxy-1,1-dimethyl-pyrrolidinium) in order to reveal any statistical alerts and predictions of those compounds over a range of end points by comparing the chemical structure with an empirical database. The analysis indicated that all three compounds should be considered negative for bacterial mutagenicity. Benzaldehyde is a well-known and naturally occurring substance. Based on available data and experience with benzaldehyde no health risk is expected at concentrations of 0.0065% as contained in the drug product GPB cream.

Taken together, topical treatment with GPB up to 2% in creams and 4% in gel was well tolerated locally and no systemic adverse effects were found. In conclusion, there are no non-clinical toxicology concerns regarding the proposed clinical use of Glycopyrronium Cantabria.

Environmental Risk Assessment (ERA)

A fragmented ERA has been provided by the Applicant which is not considered sufficient for conclusions on the potential environmental risks posed by Glycopyrronium Cantabria. The log Kow has been determined experimentally to -1.32 at a single pH. As the substance will be in the non-ionized form across all relevant pH levels it was considered appropriate that measurements were only performed at a single pH (5.7).

The ERA Phase II programme is not complete why no conclusions can be made regarding the potential environmental risks posed by Glycopyrronium Cantabria. The Applicant has presented the studies planned for completion of the ERA in Table 9 of the AR. Further studies may also be needed pending the results of the above studies, in accordance with the ERA guideline.
The completed studies, including an updated ERA, should be provided as a Type II variation. The applicant provided a commitment letter including a list of planned ERA studies. The commitment

letter also included timelines for each individual study and a statement that relevant documents will be updated and submitted via type II variation asap, but not later than Q2 2024. The issue is considered resolved within current procedure. The ERA studies will be assessed in indicated type II variation.

Summary of main study results

Substance (INN/Invented Name):					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log Kow = -1.32 at pH 5.7			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}				B/not B
	BCF				B/not B
Persistence	DT50 or ready biodegradability				P/not P
Toxicity	NOEC or CMR				T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)		µg/L			> 0.01 threshold (Y/N)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} =			List all values
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = $DT_{50,\ sediment}$ = $DT_{50,\ whole\ system}$ = % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	species
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/ kg	

Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/ kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/ kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/ kg	
Sediment dwelling organism		NOEC		mg/ kg	species

IV. CLINICAL ASPECTS

Pharmacokinetics
In one of the three clinical studies (Phase 1b, Hyp-02/2015) the applicant investigated the pharmacokinetics of GP cream. The systemic plasma exposure is relevant for safety but do not correlate to efficacy since the GP cream is locally applied and locally acting. The in vivo study was supported with literature data on absorption, distribution, metabolism, excretion, special populations, interactions and for comparison of systemic exposure with other routes of administration as well as another topically applied GP product.

Absorption:

Study Hyp-02/2015
The study was a single-center, double-blind, randomized, placebo-controlled, phase Ib, single and multiple dose escalation study to assess safety, local tolerability, PK and efficacy of GP in male and female subjects with moderate to severe axillary hyperhidrosis. The PK of GP creams containing different concentrations, i.e. 0.5%, 1%, 2%, (corresponding to 4.3 mg, 8,6 mg and 17.3 mg, respectively) was investigated in 30 adult patients with moderate to severe primary axillary hyperhidrosis. Patients were treated with ascending doses of GP in 3 cohorts, where Cohort 1 received 0.5% GP cream, Cohort 2 received 1% GP cream, and Cohort 3 received 2% GP cream. Each cohort also included placebo patients and consisted of 10 patients (8 active and 2 placebo [=vehicle]). Study drug was administered as single daily doses of 0.54 g cream to each axilla (total 1.08 g cream) for 14 days. Blood samples for assessment of plasma GP concentrations were collected up to 7 days after the first dose, on Day 14 up to 8 hours post- dose, and on Day 21 (i.e. 7 days post last dose).

Results:

Table. Pharmacokinetic parameters of GP on Day 1 (calculated by non-compartmental methods) (n=8)

Dose	**0.5%**	**1%**	**2%**
AUCz (h*pg/mL)	45.331±24.0830 (19.84/50.994/79.77)	105.833±77.2494 (36.19/92.661/270.21)	373.032±345.4567 (79.94/235.290/1103.22)
AUC_8 (h*pg/mL)	12.728±4.0737 (6.85/12.235/16.91)	40.243±25.0212 (19.85/34.490/93.75)	142.478±119.6182 (27.06/87.130/344.00)
AUC_{24} (h*pg/mL)	45.560±24.2740 (19.97/51.115/80.43)	106.513±77.7982 (36.36/93.216/272.07)	375.346±347.6475 (80.50/236.315/1110.40)
C_{max} (pg/mL)	2.234±1.3496 (0.50/2.395/4.04)	10.763±7.2854 (4.22/7.435/23.50)	29.330±26.2451 (5.21/14.300/71.20)
T_{max} (h)	7.6±10.11 (1/2.5/24)	4.0±1.60 (2/3.5/7)	2.9±1.68 (1/2.0/6)

T_z (h)	17.93±9.325 (4.0/23.83/24.0)	21.86±5.599 (8.0/23.83/23.9)	23.84±0.006 (23.8/23.83/23.9)

mean±SD (min/median/max)

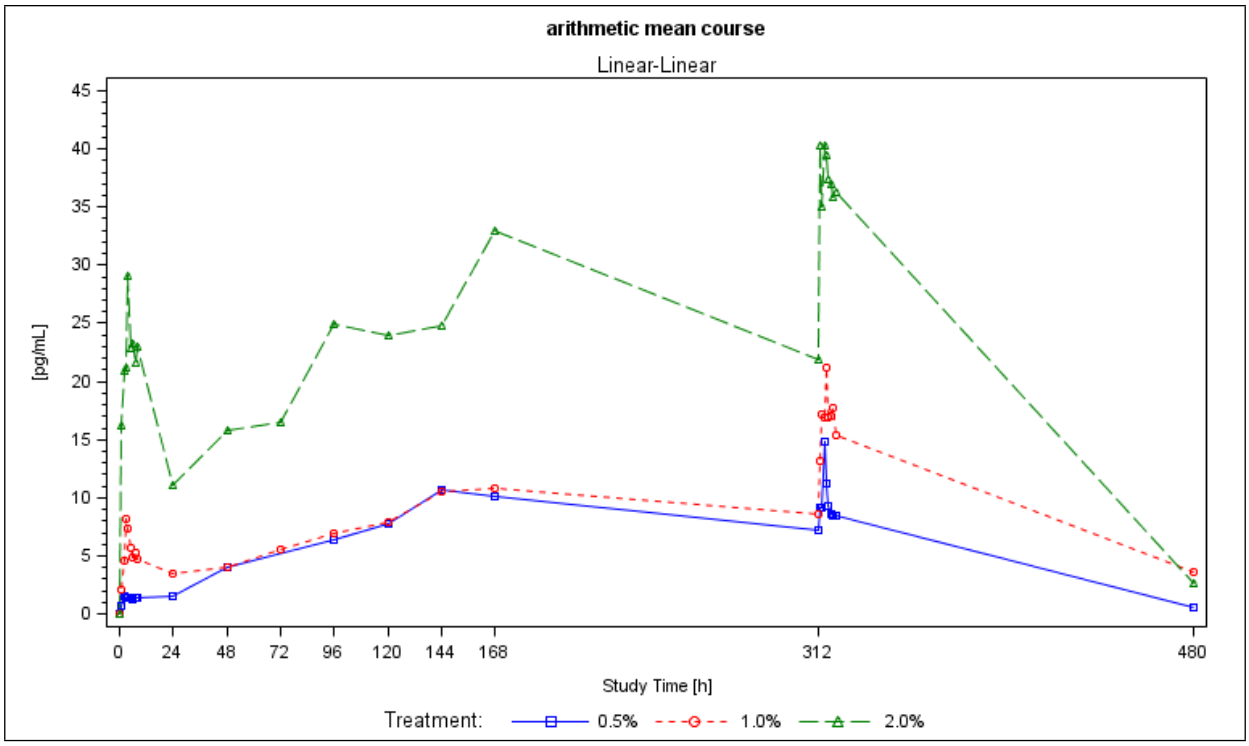
Table. Pharmacokinetic parameters of GP on Day 14 (calculated by non-compartmental methods) (n=8)

Dose	**0.5%**	**1%**	**2%**
AUC_z (h*pg/mL)	78.577±74.2848 (7.58/57.920/207.82)	128.850±94.6994 (42.50/90.065/259.90)	294.297±123.0838 (95.08/291.850/478.60)
AUC_8 (h*pg/mL)	78.577±74.2848 (7.58/57.920/207.82)	128.608±94.6254 (42.50/90.065/259.90)	294.297±123.0838 (95.08/291.850/478.60)
C_{max} (pg/mL)	18.120±21.0008 (1.19/9.170/62.40)	24.390±15.2328 (8.65/24.100/42.20)	51.875±21.4319 (17.40/51.200/80.60)
T_{max} (h)	4.1±1.75 (1/4.0/7)	3.7±2.57 (0/4.0/7)	3.1±2.36 (1/3.0/8)
T_z (h)	8.00±0.000 (8.0/8.00/8.0)	8.01±0.031 (8.0/8.00/8.1)	8.00±0.000 (8.0/8.00/8.0)
Rac	8.618±6.8600 (1.61/9.694/16.99)	2.967±1.5688 (1.52/2.574/6.12)	3.593±2.6646 (0.69/3.820/7.48)

Mean±SD (min/median/max)

The plasma exposure generally increased with dose and some accumulation was observed between Day 1 and Day 14 exposure. However, the plasma concentrations of GP cream were overall low, and after 14 days of treatment with the 1% GP cream, an $AUC_{0\text{-}8h}$ of 0.129 ng.h/mL and a C_{max} of 0.024 ng/mL was observed. Between 168h and 312h there is no increase in C_{trough} indicating that steady state is reached and that no further accumulation is expected. The inter-individual variability was high on day 1 and day 14 for both AUC and C_{max} at all investigated strengths of GP cream. There was insufficient data to characterize the elimination rate and half-life of the GP cream. Providing some information regarding elimination, the plasma concentrations 7 days post dose are very low and shows that GP is almost completely eliminated.

Figure. Mean plasma concentrations of time profiles of glycopyrronium, Day 1 to Day 21


arithmetic mean course
Linear-Linear
[pg/mL]
45
40
35
30
25
20
15
10
5
0
0
24
48
72
96
120
144
168
312
480
Study Time [h]
Treatment:
0.5%
1.0%
2.0%

Absorption of GP from other routes of administration (published data)

Comparative exposure of 1% GP cream versus iv, oral and inhaled GP formulations
The applicant has compared the exposure of 1% GP cream versus i.v., i.m., oral and inhaled GP formulations. The AUC_{0-8h} of 0.129 ng.h/mL and C_{max} of 0.024 ng/mL for the 1% GP cream after 14 days of treatment is clearly lower compared to all systemically administered GP products presented by the applicant. The difference in exposure with the inhaled GP product was clear but not as large. In general, the comparison of the area under the concentration time curve (AUC) is complicated by the fact that AUC was assessed in different studies and not over the same timeframe. However, as could be expected with the 1% GP cream being a locally applied, locally acting drug, both total and maximum exposure were low.

Comparative exposure of 1% GP cream versus topically administered GP (Qbrexza)
The PK data of the 1% GP cream was also compared to Qbrexa (approvd in the US, but not in EU), a topically applied product indicated for primary hyperhidrosis in adults and children. When comparing the PK data of the 1% GP cream with Qbrexza, the exposure was similar.

Elimination: Literature data show that renal elimination of unchanged drug appears to be the major elimination pathway of GP. After intravenous administration of radioactively labelled glycopyrronium to adults, the glycopyrronium was mainly excreted via the kidneys (85%) and to a lesser extent (< 5%) via the bile. Both in bile and in urine over 80% of the radioactivity corresponded to unchanged glycopyrrolate. Overall, the data suggest that metabolism appears to be a minor elimination route.

Special populations
No clinical studies of GP cream investigating PK in special populations have been conducted. The data on special populations is retrieved from literature.

In renally-impaired patients, the elimination of i.v. administered GP (4 μg/kg) is severely impaired. Compared to control patients, a significantly smaller plasma clearance, longer elimination $t_{1/2}$ and larger AUC were reported. While the 24 h renal excretion was 65% in control patients, it was only 7% in uremic patients.

Glycopyrronium is predominantly cleared by renal excretion and therefore no major increase in exposure to the active substance is to be expected in patients with hepatic impairment.

The safety and efficacy in patients above 65 years has not been established for the product applied for.

No clinical studies investigating PK have been made in children for the product applied for. Published data indicate that the PK of GP is not dependent on age.

Interactions:
No clinical pharmacokinetic interaction studies have been performed.

Effects of GP on enzymes and transporters: GP has no or only slight properties to induce or inhibit CYP enzymes and ABC as well as OCT transporters. Given the low systemic exposure, no inhibition or induction is expected after topical 1% GP exposure.

Effect of other drugs on GP pharmacokinetics: GP is mainly eliminated renally and therefore no effect of enzyme inhibitors or inducers is expected.

Discussion on pharmacokinetics
GP is a well-known active substance used in several indications and different routes of administration. The applicant has presented literature data exploring several of these. The comparison of the area under the curve (AUC) is not optimal since it the data is retrieved from different studies and was not assessed over the same timeframe. However, comparing the data provides a general idea on the extent

of exposure. The systemic exposure of topically administered GP cream was considerably lower compared to i.v., i.m. and orally administered formulations. In conclusion, the systemic uptake from the GP cream has been shown to be lower or similar compared to the systemic GP exposure reported for the two examples of inhaled or topically applied GP products presented by the Applicant. Since these are products with relatively few reported systemic anticholinergic side effects this supports the observed benign safety profile of the product applied for observed in the phase 3 study.

The SmPC has been adequately updated.

Pharmacodynamics
Glycopyrronium is an anticholinergic agent that blocks the action of the neurotransmitter acetylcholine at the muscarinic acetylcholine receptors, mostly at the muscarinic subtype M3 receptor. Glycopyrronium can be formulated with various salts, in this case the bromide salt, however it is the glycopyrronium molecule in itself that is pharmacologically active.

The clinical experience with glycopyrronium is extensive, for systemic treatment of severe sialorrhea, and for pre-operative reduction of salivary tracheobronchial and pharyngeal secretions both indications approved in children and adults. Glycopyrronium formulated as inhalation powder is approved for maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease.

Topical glycopyrronium formulated with the tosylate salt (Qbrexza®) is approved in the US as cloth for treatment of primary axillary hyperhidrosis from the age of 9 years old. The cloth has been recently authorized in Japan (Rapifort® Wipes 2.5%). In 2020 another anticholinergic agent, sofpironium bromide containing gel (ECCLOCK® gel 5%), was approved for treatment of primary axillary hyperhidrosis in Japan.

This product Glycopyrronium Cantabria contains glycopyrronium bromide formulated as a cream, proposed to be indicated in primary axillary hyperhidrosis from 12 years of age.

Clinical efficacy

Design and conduct of clinical studies

The present application concerns a cream formulation of 1% glycopyrronium bromide (GPB) for topical administration to reduce axillary hyperhidrosis. Heavy axillary perspiration has been linked to dysregulation of the autonomous nervous system, it starts during puberty, and causes psychological distress in affected individuals. The proposed indication is primary axillary hyperhidrosis in adults and adolescents aged 12 years and older.

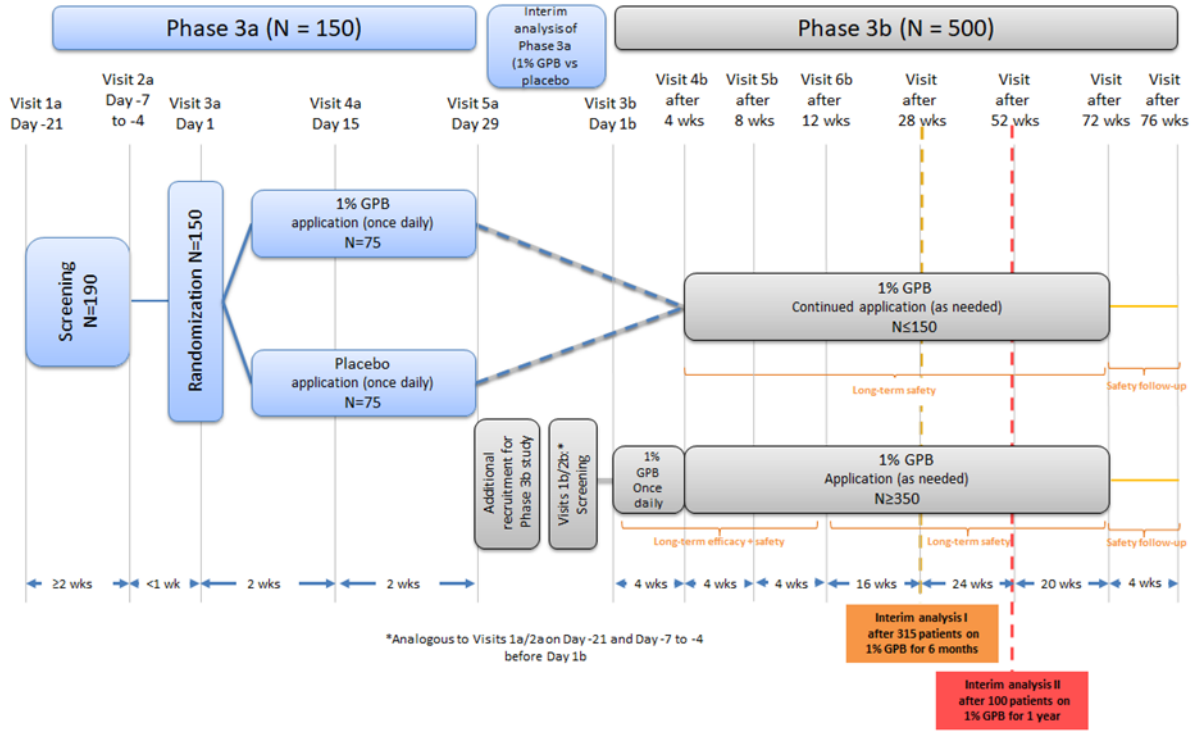
The application is supported by one Phase 1b dose-response study (Hyp-02/2015), and one Phase 3 study (Hyp1-18/2016).

Dose-finding Phase 1b study Hyp-02/2015
Study Hyp-02/2015 is a single-centre, randomized, placebo-controlled, double-blind, escalating dose study in patients with primary axillary hyperhidrosis investigating three different concentrations of GPB creams, 0.5%, 1% and 2 %.

Subjects received topical doses of either GPB creams or placebo cream for 2 weeks once daily. In the first 8 days, the study drugs were administered in the Phase 1 unit by study personnel, while in the following 6 days, study drugs were self-administered by the patients at home.
The objectives of the study were to assess the safety, tolerability, PK, and efficacy of escalating concentrations of GPB in patients with axillary hyperhidrosis.

Eligible were adult patients, aged 18-65 years, with moderate to severe primary axillary hyperhidrosis. Efficacy assessments included gravimetry (GM) of sweat production (performed pre-dose, and at Day 2, 3, 4, 8, 14 and 21), assessment of the Hyperhidrosis Disease Severity Scale (HDSS) (performed pre-dose, and at Day 2, 3, 4, 5, 6, 8, 14 and 21), and the QoL questionnaires Dermatology Life Quality Index (DLQI) and Hyperhidrosis Quality of Life index (HidroQoL) performed pre-dose, and at Day 8, 14 and 21.

Phase 3 study Hyp1-18/2016
Study Hyp1-18/2016 is a multi-center, randomized, double-blind and placebo-controlled Phase 3 study that consists of two phases. The first part of the study, Phase 3a, evaluated efficacy and safety of 1% GPB 1% cream compared with placebo for 4 weeks and is completed. The long-term safety and efficacy part, Phase 3b, is presently ongoing, with interim parts of the results presented in this Assessment Report.
In Phase 3a, patients self-administered the study drug, 1% GPB cream or placebo cream, to both axillae once daily preferably in the evening for 4 weeks. In Phase 3b, newly enrolled patients (including placebo patients from Phase 3a) self-administered 1% GPB cream to both axillae once daily for 4 weeks. After 4 weeks initial daily dose administration, all patients, administered the 1% GPB cream as-needed (at least twice per week and not more than once daily) until Week 72 (see figure of the study design below).



Note: The primary endpoint and 2 of the 3 key secondary endpoints were assessed at Week 12 in Phase 3b, with additional efficacy assessments for the remaining treatment period.
Source: Hyp1-18/2016_3b, Figure 1

Figure 1. Study Hyp1-18/2016

Patients were instructed to press the pump head of the dispenser twice to release 0.54 g (2 x 0.27 g) of cream for each axilla, i.e. a total of 1.08 g of cream per application day. The subjects treated themselves with the test products at home, which is reasonable considering the disease to be treated and the nature of the product (topical cream formulation). Treatment compliance was verified through a combination of unused investigational product returned by the subject every 4 weeks, if possible, review of the dosing diary, and discussion with the subject.

The objectives of the study were the assessment of efficacy and safety of 1% GPB cream or placebo (Phase 3a part), and the assessment of long-term efficacy and safety of 1% GPB cream in patients with primary axillary hyperhidrosis (Phase 3b part).

Eligible were adult patients, aged 18-65 years (based on inclusion criteria), with a diagnosis of severe primary axillary hyperhidrosis according to the Hyperhidrosis Disease Severity Scale (HDSS) score of 3 or 4, with at least 50 mg of sweat production in each axilla measured gravimetrically at room temperature over a 5-minute period. Patients with secondary hyperhidrosis were excluded from the studies. The inclusion and exclusion criteria are considered adequate to reflect the proposed therapeutic indication. However, no adolescents were included in the performed Phase 3 study although an indication from the age 12 is proposed.

The primary efficacy endpoint in Phase 3a was the absolute change in sweat production assessed by gravimetry at day 29 in the 1% GPB cream group compared with the placebo group. The primary efficacy endpoint in Phase 3b was the absolute change in total sweat production at week 12 (Interim Analysis I and II). This primary efficacy endpoint is of clinical relevance if met.

The key secondary endpoints in Phase 3a were 1) the percent of responders assessed by the HDSS scale (≥2-point improvement from baseline) and 2) the absolute change in the Hyperhidrosis quality of life index (HidroQoL) from baseline to Day 29 in the 1% GPB group compared with the placebo group.
The key secondary efficacy endpoints in Phase 3b were 1) the percentage of responders assessed by the HDSS (≥2-point improvement from baseline) at week 12, 2) the percentage of responders assessed by the HDSS (≥2-point improvement from baseline) at week 28 and 3) the absolute change in the HidroQoL from baseline to Week 12. All key secondary endpoints have a clinical relevance if met. Moreover, several other secondary endpoints were investigated.

The study objectives and outcomes are considered adequate for clinical studies evaluating a new product with the proposed therapeutic indication axillary hyperhidrosis. The number of subjects included in the pivotal Phase 3 study and the duration of treatment are considered relevant. The study has a comparative design to placebo in Phase 3a, and an open label design in Phase 3b. Hence, there was an objective related to superiority and randomisation and blinding were necessary. The study design is overall accepted.

Statistical aspects
Due to the skewed distribution of change from baseline in total sweat production data is analysed as the logarithm of the absolute values. This was pre-specified in the study protocol. This means that the results are presented on a relative scale and not on an absolute scale of sweat reduction.

The primary endpoint is analysed using a mixed effects model was used with treatment and logarithmic baseline values as fixed effects and center as random effect to test the primary hypothesis on a significance level of 5% ($\alpha = 0.05$; 2-sided). LSmeans estimates (with standard error and 2-sided 95% CIs) were provided for both treatment groups and for the difference between the treatments. 95% CIs were based on t-type confidence limits for each of the LSmeans. As the outcome is on the logarithmic scale, the estimates regarding the treatment effect and the least squares mean (LSmean) for the 1% GPB group and the placebo group were back-transformed leading to estimates in relative terms.

The primary analysis does not include any imputation techniques for missing data, instead observed cases are analysed. This analysis often results in overestimating of efficacy. The primary analysis is considered fairly robust since the amount of missing data is limited and the sensitivity analyses are supportive of the primary analysis, except the conservative approach using maximum observed change (i.e. the greatest change in sweat production) from baseline across groups for placebo and missing values in the 1% GPB group replaced by 0. No further sensitivity analyses are requested.

Part a and part b are analysed as independent studies with an alpha level of 0.05 for each part. This is acceptable since only part A will be considered to provide confirmatory evidence. Part B is an uncontrolled part of the study to collect long term data for efficacy and safety.

Efficacy data and additional analyses

Dose-finding Phase 1b study Hyp-02/2015

The Phase 1b study is a single center study performed in Germany in adult individuals with primary axillary hyperhidrosis. A total of 30 patients were randomized and treated with the GPB creams 0.5%, 1% or 2% (n=8 per dose cohort) or placebo (n=2 per cohort; n=10 overall). All 30 patients completed the dosing regimen as specified in the protocol, i.e. all patients received the study products (GPB or placebo) once daily over 14 days.

All study patients were white. In the GPB treated groups, most patients were male, while in the placebo group the majority were female. The patients' median age was lower in the placebo group compared with the GPB groups (30 years versus 38, 45 and 51 years). The oldest patient was 65 years, and the youngest 22 years of age. BMI was similar across treatment groups. Disease severity at baseline differed between treatment groups. In the placebo group, the mean sweat production at baseline was markedly lower compared with the GPB treated groups (187 mg in placebo group versus 322-421 mg across GPB groups). Moreover, the patient reported outcome scores were unbalanced across the treatment groups.

Efficacy results – Phase 1b study Hyp-02/2015

The efficacy variable responders assessed by gravimetry demonstrated a similar reduction in sweat production at Day 8 and Day 14 in all GPB cream treated groups, both in absolute number (mg) and percent change from baseline. The mean percent reduction in sweat production from baseline at Day 14 was -79% (SD 30.2) in the 0.5% GPB group, -80% (SD 8.2) in the 1% GPB group and -90% (SD 9.0) in the 2% GPB group, respectively. In the placebo group, sweat production was reduced with -53.7% (SD 18.7) compared with baseline. A clinical efficacy of GPB compared with placebo was demonstrated. No clear dose-response could be demonstrated, which might be due to the small number of patients exposed to study drug (n=8) and most likely also to the unbalanced disease severity noted in the treatment groups at baseline.

Results obtained with the patient reported outcomes HDSS, HidroQoL and change in Dermatology life quality index questionnaire (DLQI) showed slight improvement in disease severity and QoL which was more pronounced with 1% GPB and 2% GPB compared with the 0.5% cream formulation.

Phase 3 study Hyp1-18/2016

The Phase 3a study Hyp1-18/2016 was performed at 21 centres, and the Phase 3b part at 37 centres in the EU. In Phase 3a, study completion was high, only five subjects discontinued prematurely. Three subjects treated with 1% GPB discontinued (1 patient each due to withdrawal of consent, lost to follow-up, and "other reasons", i.e. not being convinced of the treatment's efficacy) and 2 subjects treated with placebo (1 patient each due to "other reasons", i.e. lack of efficacy, and being lost to follow-up). In Phase 3b, 17.6% had discontinued treatment at week 28 (Interim Analysis I), and 13.5% had discontinued treatment when the Interim Analysis II was completed at week 52. The primary reasons for discontinuation in both analyses were withdrawal of consent, adverse event and lost to follow up.

Important protocol deviations were reported in Phase 3a in the category of premature termination, time window violation, deviations in the GM procedure, product use (too little of the test product) and eligibility violations. In Phase 3b similar protocol deviation were reported, and in addition also use of aluminium chloride-containing deodorant and medical history. None of the protocol deviations are thought to seriously affect the evaluation of efficacy or safety results of the study.

The Full Analysis Set of Phase 3a (FASa) population comprised 171 subjects and the Per Protocol Set Phase 3a (PPSa) population comprised 127 subjects.

The Full Analysis Set of Phase 3b (FASb) population in Interim Analysis I comprised 315 patients, which included 143 patients that rolled over from Phase 3a, and 172 newly recruited patients (FASnewb). The Per Protocol Set Phase 3b (PPSa) population comprised 242 subjects and PPSnewb 121 patients. The 100 patients who completed 1 year of treatment (Week 52 visit) constituted the FASb analysis set in Interim Analysis II.

Demographic and baseline characteristics of Phase 3a showed an equal number of male and females, mostly white individuals with mean age of 36 years (range 18-65). The sweat production at baseline was slightly higher in the GPB 1% cream group compared with placebo. In the HDSS questionnaire the patients thought their underarm sweating barely tolerable and frequently interfering with their daily activities (score 3), or intolerable and always interferes with their daily activities (score 4) indicating severe hyperhidrosis. In the GPB 1% cream group, approximately 50% rated either score 3 or 4, while in the placebo group, approximately 40% rated score 3 and 60% rated score 4.

Demographic and baseline characteristics of Phase 3b only concern the newly recruited patients. There was a slight majority of female patients in Phase 3b. Almost all were white and median age was 35 years (range 18-65). Disease severity was like Phase 3a. HDSS at baseline was grade 3 for 60% and grade 4 for 40% of patients included in Phase 3b.

Efficacy results – Phase 3a part of study Hyp1-18/2016
In the Phase 3a part of study Hyp1-18/2016, the primary endpoint was absolute change in sweat production assessed by gravimetry at day 29 in the 1% GPB cream group compared with the placebo group. The GPB 1% cream was significantly superior ($p = 0.0038$) compared with treatment with its cream vehicle and thus met the primary endpoint. The absolute reduction in sweat production from baseline to Day 29 was reduced with -64% in the 1% GPB group compared with -29% in the placebo group when evaluated at Day 29.

Table 1. Absolute change in sweat production from baseline to Day 29 in study Hyp1-18/2016 Phase 3 (FASa, PPSa)

	FASa N=171		PPSa N=127	
	1% GPB N=87	**Placebo N=84**	**1% GPB N=69**	**Placebo N=58**
Absolute values (mg), mean (SD)				
Baseline	306.97 (249.33)	284.64 (212.47)	312.87 (259.87)	277.51 (198.04)
Change to Day 29	-197.08 (252.41)[a]	-83.49 (168.21)[b]	-198.19 (254.02)[c]	-57.45 (150.53)[d]
Logarithmic values, mean (SD)				
Baseline	5.31 (1.20)	5.32 (0.92)	5.30 (1.29)	5.34 (0.86)
Change to Day 29	-1.58 (1.87)[a]	-0.72 (1.55)[b]	-1.40 (1.57)[c]	-0.53 (1.21)[d]
Mixed effects model for change from baseline				
LSmeans (95% CI)	-1.56 (-1.94; -1.18)	-0.75 (-1.13; -0.37)	-1.39 (-1.76; -1.02)	-0.53 (-0.94; -0.13)
p-value[e]	<0.0001	0.0002	<0.0001	0.0099
Difference to placebo				
LSmeans (95% CI)	-0.81 (-1.35; -0.27)		-0.86 (-1.37; -0.35)	
p-value[e]	0.0038		0.0013	

Data available for: [a] N=77, [b] N=78, [c] N=65, [d] N=55.
[e] 2-sided, $\alpha = 0.05$.
CI=confidence interval, FASa=Full Analysis Set (Phase 3a), GPB=glycopyrronium bromide, LSmeans=least square means, N=number of patients, PPSa=Per-Protocol Set (Phase 3a), SD=standard deviation.
Source: Hyp1-18/2016_3a, Table 4.1.1.

Sensitivity analysis I can be viewed as a worst-case scenario where placebo-treated patients with missing data were imputed with the best observed result in the placebo group. Patients in the GPB group had missing data imputed with 0, which implies no change. Sensitivity analysis I is not supporting a positive effect of GPB but sensitivity analysis II results in similar results as the analyses based on FASa and PPSa data using observed cases (primary analysis).

Table 2. Absolute change in sweat production (mg) from baseline to Day 29 - sensitivity analyses I and II in study Hyp1-18/2016 Phase 3a (PPSa)

	Sensitivity Analysis I		Sensitivity Analysis II	
	1% GPB N=69	**Placebo N=58**	**1% GPB N=69**	**Placebo N=58**
Logarithmic values, mean (SD)				
Baseline	5.30 (1.29)	5.34 (0.86)	5.30 (1.29)	5.34 (0.86)
Change to Day 29	-1.32 (1.56)	-0.86 (1.87)	-1.32 (1.56)	-0.50 (1.18)
Mixed effects model for change from baseline				
LSmeans (95% CI)	-1.33 (-1.75; -0.91)	-0.86 (-1.31; -0.41)	-1.33 (-1.68; -0.97)	-0.49 (-0.87; -0.10)
p-value[a]	<0.0001	0.0003	<0.0001	0.0134
Difference to placebo				
LSmeans (95% CI)	-0.47 (-1.06; 0.12)		-0.84 (-1.33; -0.35)	
p-value[a]	0.1189		0.0009	

Sensitivity Analysis I: Missing values for the change from baseline were imputed by the largest observed change in the placebo group, and by 0 in the 1% GPB group.
Sensitivity Analysis II: Missing values for the change from baseline were imputed by 0 in both treatment groups.
[a] 2-sided, α = 0.05.
CI=confidence interval, GPB=glycopyrronium bromide, LSmeans=least square means, N=number of patients, PPSa=Per Protocol Set (Phase 3a), SD=standard deviation.
Source: Hyp1-18/2016_3a, Table 4.1.1, Table 4.1.2, Table 4.1.3.

Various post-hoc analyses were conducted to explore distribution of data; different responder definitions and subgroups were performed. These analyses are considered exploratory, but the results are considered consistent with the primary analysis.

In the key secondary endpoint assessing responders in HDSS score, about 2 times as many patients responded (i.e., showed an improvement of 2 or more points of the HDSS) to treatment with 1% GPB than to treatment with placebo; the difference approached statistical significance (p = 0.0542). The second key secondary endpoint assessing absolute changes in the HidroQoL total score, the median improvement in HidroQoL total score was larger in the 1% GPB than in the placebo group (median difference to placebo of -5.0, p <0.0001). For all other secondary endpoints, the results overall supported the results obtained with the primary and key secondary endpoints in Phase 3a.

Table 3. Percentage of HDSS responders at Day 29 in study Hyp1-18/2016 Phase 3a (FASa, PPSa)

	FASa N = 171		PPSa N = 127	
	1% GPB N=87	**Placebo N=84**	**1% GPB N=69**	**Placebo N=58**
Responder rate, n (%)[a]	20 (23.0)	10 (11.9)	19 (27.5)	7 (12.1)
Difference to placebo[b]	n=171		n=127	
Odds ratio (95% CI)	0.44 (0.19; 1.03)		0.29 (0.10; 0.85)	
p-value[c]	0.0542		0.0174	

Responders were defined as patients with ≥2-point improvement from baseline.
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.
[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 analysis, PPSa=Per Protocol Set (Phase 3a).
Source: Hyp1-18/2016_3a, Table 4.2.1.

Table 4. Change in HidroQoL from baseline to Day 29 in study Hyp1-18/2016 Phase 3a (FASa, PPSa)

	FASa N = 171		PPSa N = 127	
	1% GPB N=87	**Placebo N=84**	**1% GPB N=69**	**Placebo N=58**
Total score, median (range)				
Baseline	29.0 (10 - 36)	30.0 (11 - 36)[b]	29.0 (10 - 36)	29.0 (14 - 36)[d]
Change to Day 29	-6.0 (-36 - 6)[a]	-1.0 (-35 - 4)[c]	-6.0 (-36 - 6)	-1.0 (-35 - 4)[d]
Difference to placebo[e]	n=163		n=125	
Median (95% CI)	-5.0 (-6.0; -2.0)		-5.0 (-6.0; -1.0)	
p-value[f]	<0.0001		0.0045	
Daily life activities domain score, median (range)				
Baseline	11.0 (3 - 12)	10.0 (2 - 12)[b]	11.0 (3 - 12)	10.0 (6 - 12)[d]
Change to Day 29	-3.0 (-12 - 2)[a]	-1.0 (-11 - 2)[c]	-2.0 (-12 - 2)	-1.0 (-11 - 2)[d]
Difference to placebo[e]	n=163		n=125	
Median (95% CI)	-2.0 (-3.0; -1.0)		-1.0 (-3.0; -1.0)	
p-value[f]	<0.0001		0.0007	
Psychosocial domain score, median (range)				
Baseline	18.0 (7 - 24)	19.0 (8 - 24)[b]	19.0 (7 - 24)	18.5 (8 - 24)[d]
Change to Day 29	-3.5 (-24 - 6)[a]	-1.0 (-24 - 3)[c]	-3.0 (-24 - 6)	-1.0 (-24 - 3)[d]
Difference to placebo[e]	n=163		n=125	
Median (95% CI)	-2.5 (-3.0; -1.0)		-2.0 (-3.0; 0.0)	
p-value[f]	0.0006		0.0292	

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.

[f] 2-sided, $\alpha = 0.05$.

CI=confidence interval, FASa=Full Analysis Set (Phase 3a), GPB=glycopyrronium bromide, HidroQoL=hyperhidrosis quality of life, N=number of patients, n=number of patients in the analysis, PPSa=Per Protocol Set (Phase 3a).

Source: Hyp1-18/2016_3a, Table 4.2.2.

Efficacy results – Phase 3b part of study Hyp1-18/2016

The patients included in Phase 3b consisted of those who were rolled over from Phase 3a, both GPB treated patients and placebo treated patients. Moreover, newly recruited patients were included in Phase 3b. All patients not previously exposed to the GPB cream were treated for one month with daily application of the test product and were then allowed to use the product as needed but not less than twice per week to achieve a sufficient reduction in sweat production.

In the Interim analysis I after 12 weeks of treatment, a change from baseline of -58% was obtained in absolute values (mg) both in the FAS (n=172) and PPS (n=121) population of newly recruited patients.

Table 5. Absolute change in sweat production from baseline to Week 12 in study Hyp1-18/2016 Phase 3b, Interim Analysis I (FASnewb, PPSnewb)

	1% GPB FASnewb N=172	1% GPB PPSnewb N=121
Absolute values (mg), mean (SD)		
Baseline	276.09 (230.34)	286.41 (215.40)
Change to Week 12	-161.29 (222.51)[a]	-167.28 (215.23)[b]
Logarithmic values, mean (SD)		
Baseline	5.220 (1.075)	5.268 (1.128)
Change to Week 12	-1.573 (2.115)[a]	-1.534 (2.187)[b]
Mixed effects model for the change from baseline (logarithmic values)		
Estimate (97.06% CI)	-1.536 (-1.979, -1.092)[a]	-1.497 (-1.952, -1.041)[b]
p-value[c]	<0.0001	<0.0001
Ratio Week 12 versus baseline (97.06% CI), back transformed	0.215 (0.138, 0.336)	0.224 (0.142, 0.353)

Missing baseline values of total sweat production were replaced with valid values from the (repeated) gravimetric measurement at Screening. Missing Week 12 values of total sweat production were replaced (if available) with values from the gravimetric measurement at Week 4.
Data available for [a] N = 168, [b] N = 117.
[c] 2-sided, $\alpha = 0.0294$.
CI=confidence interval, FASnewb=Full Analysis Set (Phase 3b newly recruited patients), GPB=glycopyrronium bromide, N=number of patients, PPSnewb=Per-Protocol Set (Phase 3b newly recruited patients), SD=standard deviation.
Source: Hyp1-18/2016_3b, Table 4.1.1_I

The sensitivity analyses presented, consisting of a complete case analysis and 2 subgroup analyses show results consistent with the primary analysis, and as such support the conclusion drawn from the primary analysis.

For the first and second key secondary endpoint analysis assessing HDSS responders at Week 12 and 28, the proportion of responders was greater than 25% (39%, p<0.0001) at both time points, and the key secondary endpoints were met. The results from PPS analysis were very similar and confirmed the results from the FAS.

Table 6. Percentage of HDSS responders at Week 12 in study Hyp1-18/2016 Phase 3b, Interim Analysis I (FASb, PPSb)

	1% GPB FASb N=315	1% GPB PPSb N=242
Responder rate, n (%)	104 (33.0)	83 (34.3)
Proportion of responders (98.53% CI) [a]	0.33 (0.27, 0.40)	0.34 (0.27, 0.42)
p-value [b]	0.0005	0.0004

Responders were defined as patients with ≥2-point improvement from baseline.
Patients with missing values were considered non-responders.
[a] 1-sample binomial test, exact 1-sided 98.53% Clopper-Pearson CI.
[b] 1-sided, α=0.0147.
CI=confidence interval, FASb=Full Analysis Set (Phase 3b), GPB=glycopyrronium bromide, HDSS=hyperhidrosis disease severity scale, N=number of patients, PPSb=Per-Protocol Set (Phase 3b).
Source: Hyp1-18/2016_3b, Table 4.2.1_I

Table 7. Percentage of HDSS responders at Week 28 in study Hyp1-18/2016 Phase 3b, Interim Analysis I (FASb, PPSb)

	1% GPB FASb N=315	1% GPB PPSb N=242
Responder rate, n (%)	124 (39.4)	99 (40.9)
Proportion of responders (98.53% CI) [a]	0.39 (0.33, 0.46)	0.41 (0.33, 0.49)
p-value [b]	<0.0001	<0.0001

Responders were defined as patients with ≥2-point improvement from baseline.
Patients with missing values were considered non-responders.
[a] 1-sample binomial test, exact 1-sided 98.53% Clopper-Pearson CI.
[b] 1-sided, α=0.0147.
CI=confidence interval, FASb=Full Analysis Set (Phase 3b), GPB=glycopyrronium bromide, HDSS=hyperhidrosis disease severity scale, N=number of patients, PPSb=Per-Protocol Set (Phase 3b).
Source: Hyp1-18/2016_3b, Table 4.2.2_I.

For the third key secondary endpoint analysis assessing absolute changes in the HidroQoL total score and in the 2 domains thereof, the median improvements in HidroQoL total score of -12.0 points in the FASb were observed, which were statistically significant. The result for PPSb was similar and confirmed the results from the FASb.

Table 8. Change in HidroQoL from baseline to Week 12 in study Hyp1-18/2016 Phase 3b, Interim Analysis I (FASb, PPSb)

	1% GPB FASb N=315	1% GPB PPSb N=242
Total score		
Baseline (Phase 3a), median (range)	29.0 (10 - 36)	29.0 (14 - 36)
Baseline (Phase 3b), median (range)	27.0 (6 - 36)	27.0 (6 - 36)
Change to Week 12, median (range)	-12.0 (-36, 5) [a]	-13.0 (-36, 5) [b]
Median change to Week 12 (97.06% CI) [c]	-12.0 (-14.0, -10.0) [a]	-13.0 (-14.0, -11.0) [b]
p-value [d]	<0.0001	<0.0001
Daily life activities domain score		
Baseline (Phase 3a), median (range)	11.0 (2 - 12)	11.0 (4 - 12)
Baseline (Phase 3b), median (range)	10.0 (1 - 12)	10.0 (1 - 12)
Change to Week 12, median (range)	-5.0 (-12, 3) [a]	-5.0 (-12, 1) [b]
Median change to Week 12 (97.06% CI) [c]	-5.0 (-6.0, -4.0) [a]	-5.0 (-6.0, -4.0) [b]
p-value [d]	<0.0001	<0.0001
Psychosocial domain score		
Baseline (Phase 3a), median (range)	19.0 (7 - 24)	19.0 (7 - 24)
Baseline (Phase 3b), median (range)	18.0 (2 - 24)	17.5 (4 - 24)
Change to Week 12, median (range)	-7.0 (-24, 5) [a]	-8.0 (-24, 4) [b]
Median change to Week 12 (97.06% CI) [c]	-7.0 (-8.0, -6.0) [a]	-8.0 (-9.0, -6.0) [b]
p-value [d]	<0.0001	<0.0001

[a] N=310.
[b] N=239.
[c] Two-sided Wilcoxon signed rank test with 97.06% Hahn-Meeker CIs.
[d] 2-sided, $\alpha = 0.0294$.
For the roll-over patients from Phase 3a (N=143), the baseline value was assessed during Phase 3a, see "Baseline (Phase3a)".
For the newly recruited patients (N=172), the baseline value was assessed at baseline for Phase3b, see "Baseline (Phase3b)".
Patients who rolled over from the Phase 3a part joined the Phase 3b part of the study after Week 4.
CI=confidence interval, FASb=Full Analysis Set (Phase 3b), GPB=glycopyrronium bromide, HidroQoL=hyperhidrosis quality of life, N=number of patients, PPSb=Per-Protocol Set (Phase 3b).
Source: Hyp1-18/2016_3b, Table 4.2.3_I.

Two additional sensitivity analyses were performed for the primary endpoint. Sensitivity analysis I can be viewed as a worst-case scenario where placebo-treated patients with missing data were imputed with the best observed result in the placebo group. Patients in the GPB group had missing data imputed with 0, which implies no change. Sensitivity analysis I is not supporting a positive effect of GPB but sensitivity analysis II results in similar results as the analyses based on FASa and PPSa data using observed cases (primary analysis)**.**

All primary and key secondary endpoints were met. For all other secondary endpoints, the results overall supported the results obtained with the primary and key secondary endpoints in Phase 3b.

Subgroup analysis
A post-hoc subgroup analyses were conducted based on data from Phase 3a for the efficacy variables sweat reduction responders and HDSS by prior treatment, sex, age (below or above 40 years of age) and BMI (below 25, between 25 to below 3 and above 30). No effect on either parameter could be noted.

In Phase 3b, post-hoc subgroup analyses were conducted for the absolute changes in total sweat production from baseline to Week 4 and Week 12 by sex and age category (i.e., ≤40 years and >40

years). Regarding sex, males showed larger reductions in sweat production than females at Week 4 (-202.21 mg versus -166.64 mg) and Week 12 (-186.15 mg versus -143.10 mg) most probably due to a higher baseline sweat production.

Regarding age, patients >40 years demonstrated larger reductions in sweat production than patients ≤ 40 years at Week 4 (-247.76 mg versus -148.48 mg) and Week 12 (-234.23 mg versus -125.80 mg). Patients in the >40-year subgroup had higher baseline sweat production compared to patients in the ≤ 40-year subgroup. Overall, these results suggest that 1% GPB cream is effective in both sexes and all age groups investigated (18-65 years of age).

Analysis performed across trials – magnitude of treatment effect
The treatment regimen in Phase 3a was identical to the regimen in the first 4 weeks of Phase 3b i.e. once daily treatment with 1% GPB cream which allowed a comparison of efficacy results for this time window. Overall, the results were very similar for Phase 3a and Phase 3b which confirms the reproducibility of the obtained results. The GPB 1% cream reduced sweat production with approximately 65-70% when evaluated at Week 4.

Table 9. Comparison of main efficacy results after 4 weeks of treatment with 1% GPB (Phase 3a versus Phase 3b of study Hyp1-18/2016)

	Phase 3a N=87 (FASa)	**Phase 3b N=172 (FASnewb)**
Absolute change in sweat production to Week 4 (mg), mean (SD)	-197.08 (252.41) (n=77)	-181.17 (197.30) (n=164)
Percentage change in sweat production to Week 4, median % (95% CI)[a]	-64.63 (-73.13; -51.75) (n=77)	-69.50 (-77.20, -61.89) (n=164)
Absolute change in HDSS to Week 4, median (range)	0.0 (-3 - 1) (n=83)	-1.0 (-3 - 1) (n=167)
Percentage of HDSS responders (≥2-point improvement) at Week 4, (%)	23.0 (n=20)	22.7 (n=39)
Absolute change in HidroQoL to Week 4, median (range)	-6.0 (-36 - 6) (n=84)	-8.0 (-36 - 5) (n=167)
Percentage of HidroQoL responders (≥4-point improvement) at Week 4, (%)	59.8 (n=87)	69.2 (n=172)
Absolute change in DLQI to Week 4, median (range)	-5.5 (0-28) (n=84)	-6.0 (-27 - 13) (n=167)

[a] 2-sided Wilcoxon rank test with 95% Hahn Meeker CIs.
CI=confidence interval, FASa=Full Analysis Set (Phase 3a), FASnewb=Full Analysis Set (Phase 3b newly recruited patients), GPB=glycopyrronium bromide, N=number of patients, n=number of patients in analysis.
Source: Module 2.7.3, Table 20, Table 23, Table 25, Table 26, Table 30, Table 39, Table 40, Table 42, Table 43, Table 47, Table 48; Hyp1-18/2016_3a, Table 4.3.5, Hyp1-18/2016_3a, Table 4.3.10.

Long-term efficacy - duration of treatment effect
Efficacy data are available up to 52 weeks with at last twice weekly administration following the initial daily dose administration for 4 weeks. The treatment effect of the 1% GPB cream is sustained with the twice weekly dose administration proposed in the SmPC. Interruption of treatment and subsequent need for retreatment has not been investigated. It is assumed that if treatment ceases, sweating will reoccur. Therefore, treatment need to continue if a continuous efficacy on axillary hyperhidrosis is wished.

Patient reported outcome tools (i.e., HidroQoL and proportion of HidroQoL responders) tended to further improve after the first 4 weeks of treatment, over the remaining treatment period.

The results of study Hyp1-18/2016 Phase 3b will be submitted when finalised, as a post approval commitment in the form of a type II variation after completion of the MAA procedure.

Conclusions on clinical efficacy
A significantly superior efficacy for Glycopyrronium Cantabria (GPB 1% cream) compared with vehicle cream was demonstrated for the primary efficacy endpoint in the pivotal phase 3 study Hyp1-18/2016. The key secondary efficacy endpoints and other endpoints supported the efficacy of Glycopyrronium Cantabria. When dosed as proposed in the SmPC, four weeks with daily administration followed with twice weekly dose administration, an approximately 60% reduction in sweating is obtained, assessed to be a clinical relevance to patients who suffer from heavy axillary hyperhidrosis. Although difficult to compare, the magnitude of efficacy of Glycopyrronium Cantabria seems to be in the same range as the US approved product Qbrexza®, containing glycopyrronium tosylate for topical treatment of axillary hyperhidrosis.

The initially proposed indication of Glycopyrronium Cantabria concerned patients from the age of 12 years old. The CMS ES objected against including adolescents in the therapeutic indication of the product. The Applicant has agreed to withdraw the inclusion of the paediatric population (age 12-17 years). Glycopyrronium Cantabria is therefore suggested to be indicated only in adults until clinical data in adolescents are available.

Overall, the efficacy documentation presented for the GPB 1% cream is considered adequate. The results of study Hyp1-18/2016 Phase 3b will be submitted when finalised, as a post approval commitment in the form of a type II variation after completion of the MAA procedure.

Clinical safety
Topical glycopyrronium bromide (GPB) 10 mg/g cream, is a synthetic muscarinic anticholinergic agent. A number of glycopyrronium products, including parenteral, oral, or inhalational formulations are approved within EU and have been used for several years in various indications. The applied indication of Glycopyrronium Cantabria is for the topical treatment of primary axillary hyperhidrosis in adults and adolescents (aged 12 years and older). The recommended dosing is two pump actuations per armpit (equivalent to 540 mg of cream per armpit) applied to each armpit evenly, once a day, preferably in the evening during the first 4 weeks of treatment. From the 5th week on, the frequency of application of GPB can be reduced to twice a week, depending on the response to treatment.

The treatment has been evaluated in adults 18-65 years of age in one Phase 1b study with GPB cream at 3 different concentrations and in a pivotal Phase 3 study with 1% GPB cream. Uncertainties as to the study procedures and outcome of study Hyp-02/2015 including relatively few involved patients receiving the 1% GPB cream, limits the value of this study from a safety perspective. The phase 3 study consisted of two parts. In part 3a, patients were randomized and treated with 1% GPB cream or placebo with evaluation of PEP at Week 4. In Part 3b PEP was assessed at Week 12 in newly recruited patients and key secondary endpoints at different time points up to Week 72. Long-term exposure has been followed for a period of up to 12 months. See table below of phase 3 study exposure.

Table 10. Overall summary of adverse events in study Hyp1-18/2016 Phase 3a (SAFa) and Phase 3b, Interim Analysis I and II (SAFb)

Study	Treatment	Dose and duration	Number of patients treated
Hyp1-18/2016 (Phase 3a part)	1% GPB	Once daily 0.54 g of cream to each axilla **Duration: 4 weeks**	87*
Hyp1-18/2016 (Phase 3b part)	1% GPB	Once daily 0.54 g of cream to each axilla for the first 4 weeks; thereafter 0.54 g of cream to each axilla as needed (at least twice per week and not exceeding once daily) **Duration: 6 months**	315** (Interim Analysis I)
	1% GPB	Once daily 0.54 g of cream to each axilla for the first 4 weeks; thereafter 0.54 g of cream to each axilla as needed (at least twice per week and not exceeding once daily) **Duration: 12 months**	100 (subset of the 315 patients treated for 6 months) (Interim Analysis II)
Hyp-02/2015 (Phase 1b)	0.5%, 1% or 2% GPB	Once daily 0.54 g of cream to each axilla **Duration: 14 days**	24 (of these, 8 patients treated with 1%)

The combined safety database of 351 patients exposed to the GPB cream, includes apart from the 315 patients of the phase 3 study exposed to the GPB 1 % cream and the 24 patients exposed to 0.5%, 1% or 2% GPB cream respectively in the phase 1b study, additionally 12 patients who were exposed to GPB 1 % cream in the initial part of phase 3 study but did not continue the long-term study. To sum up, a total of 335 patients were exposed to the applied GPB 1% cream in clinical studies. Of these 327 patients were included in the phase 3 study and 315 exposed for six months and a subset of 100 exposed for 1 year. The long-term study is still ongoing. The extent of exposure is considered satisfactory considering previous experience of glycopyrronium products including topical administration and the safety profile from that perspective is considered rather well characterised.

Adverse events

Table 11. Overall summary of adverse events in study Hyp1-18/2016 Phase 3a (SAFa) and Phase 3b, Interim Analysis I and II (SAFb)

	Number of patients (%)			
	Phase 3a		Phase 3b 6-month data Interim Analysis I	Phase 3b 12-month data Interim Analysis II
	1% GPB N=87	Placebo N=84	1% GPB N=315	1% GPB N=100
Any TEAE	43 (49.4)	37 (44.0)	210 (66.7)	79 (79.0)
Drug-related TEAE*	24 (27.6)	11 (13.1)	90 (28.6)	31 (31.0)
Severe TEAE	2 (2.3)	4 (4.8)	11 (3.5)	5 (5.0)
SAE	1 (1.1)	0 (0.0)	7 (2.2)	4 (4.0)
Fatal AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)**	0 (0.0)**

In the placebo-controlled part of the pivotal phase 3 study (part a) any TEAEs overall were reported at similar frequencies in the 1% GPB cream and the placebo groups (49.4% versus 44.0%) but then again a higher percentage of 1% GPB cream patients reported drug-related TEAEs compared to placebo patients (27.6% versus 13.1%). These differences are mainly due to gastrointestinal disorders such as dry mouth and eye disorders such as dry eye/ocular hyperemia, adverse reactions in line with

anticholinergic influence.

Table 12. Common TEAEs in study Hyp1-18/2016 Phase 3a part. TEAEs occurring in 2 or more patients (corresponding to >2% of patients) in any treatment group, by SOC and PT (SAFa, N=171)

System organ class Preferred term	**Number of patients (%)**	
	1% GPB N=87	**Placebo N=84**
Any TEAE	43 (49.4)	37 (44.0)
Gastrointestinal disorders	**16 (18.4)**	**9 (10.7)**
Dry mouth	15 (17.2)	4 (4.8)
Gastritis	0 (0.0)	2 (2.4)
Infections and infestations	**15 (17.2)**	**15 (17.9)**
Nasopharyngitis	10 (11.5)	14 (16.7)
Urinary tract infection	2 (2.3)	0 (0.0)
Nervous system disorders	**11 (12.6)**	**9 (10.7)**
Headache	9 (10.3)	8 (9.5)
Dizziness	1 (1.1)	2 (2.4)
General disorders and administration site conditions	**11 (12.6)**	**6 (7.1)**
Application site erythema	5 (5.7)	4 (4.8)
Application site papules	2 (2.3)	0 (0.0)
Eye disorders	**4 (4.6)**	**1 (1.2)**
Ocular hyperaemia	2 (2.3)	0 (0.0)
Skin and subcutaneous tissue disorders	**4 (4.6)**	**5 (6.0)**
Rash papular	0 (0.0)	2 (2.4)
Injury, poisoning and procedural complications	**4 (4.6)**	**1 (1.2)**
Musculoskeletal and connective tissue disorders	**3 (3.4)**	**2 (2.4)**
Respiratory, thoracic and mediastinal disorders	**2 (2.3)**	**2 (2.4)**
Nasal dryness	2 (2.3)	0 (0.0)
Oropharyngeal pain	0 (0.0)	2 (2.4)
Ear and labyrinth disorders	**2 (2.3)**	**1 (1.2)**
Investigations	**2 (2.3)**	**0 (0.0)**
Vascular disorders	**1 (1.1)**	**2 (2.4)**
Hypertension	0 (0.0)	2 (2.4)

SAFa=Safety Analysis Set (Phase 3a), TEAE=treatment-emergent adverse event.
Sorted by descending frequency in the 1% GPB group.

Table 13. Study Hyp1-18/2016, phase 3 part b, Interim Analysis I. TEAEs occurring in ≥3% of patients in any group in Phase 3b (SAFb, N=315)

System organ class Preferred term	Number (%)[a] of patients		
	1% GPB Baseline to Week 4 N=247[b]	1% GPB After Week 4 N=315	1% GPB Baseline to Week 28 (Overall) N=315
Any TEAE	108 (43.7)	183 (58.1)	210 (66.7)
Infections and infestations	**36 (14.6)**	**102 (32.4)**	**118 (37.5)**
Nasopharyngitis	29 (11.7)	73 (23.2)	87 (27.6)
Gastrointestinal disorders	**34 (13.8)**	**41 (13.0)**	**63 (20.0)**
Dry mouth	26 (10.5)	12 (3.8)	36 (11.4)
Nervous system disorders	**24 (9.7)**	**44 (14.0)**	**60 (19.0)**
Headache	20 (8.1)	36 (11.4)	51 (16.2)
General disorders and administration site condition	**22 (8.9)**	**33 (10.5)**	**48 (15.2)**
Application site erythema	8 (3.2)	11 (3.5)	18 (5.7)
Skin and subcutaneous tissue disorders	**13 (5.3)**	**20 (6.3)**	**30 (9.5)**
Respiratory, thoracic and mediastinal disorders	**10 (4.0)**	**19 (6.0)**	**28 (8.9)**
Oropharyngeal pain	3 (1.2)	9 (2.9)	12 (3.8)
Musculoskeletal and connective tissue disorders	**5 (2.0)**	**19 (6.0)**	**23 (7.3)**
Eye disorders	**7 (2.8)**	**15 (4.8)**	**22 (7.0)**
Dry eye	3 (1.2)	10 (3.2)	13 (4.1)
Injury, poisoning and procedural complications	**8 (3.2)**	**14 (4.4)**	**22 (7.0)**
Investigations	**7 (2.8)**	**8 (2.5)**	**15 (4.8)**

[a] Percentages are based on the number of patients in each analysis group.

[b] Patients receiving placebo in Phase 3a are not included.

GPB=glycopyrronium bromide, SAFb=Safety Analysis Set (Phase 3b), TEAE=treatment-emergent adverse event.
Sorted by descending frequency in the 1% GPB overall group.

Table 14. TEAEs occurring in ≥3% of patients in any group in study Hyp1-18/2016 Phase 3b, Interim Analysis II (SAFb, N=100)

System organ class Preferred term	Number (%)[a] of patients		
	1% GPB Baseline to Week 4 N=54[b]	1% GPB After Week 4 N=100	1% GPB Baseline to Week 52 (Overall) N=100
Any TEAE	30 (55.6)	73 (73.0)	79 (79.0)
Infections and infestations	**10 (18.5)**	**44 (44.0)**	**49 (49.0)**
Nasopharyngitis	7 (13.0)	33 (33.0)	38 (38.0)
Conjunctivitis	0 (0.0)	3 (3.0)	3 (3.0)
General disorders and administration site conditions	**10 (18.5)**	**16 (16.0)**	**24 (24.0)**
Application site erythema	6 (11.1)	8 (8.0)	13 (13.0)
Application site pruritus	1 (1.9)	3 (3.0)	4 (4.0)
Application site papules	2 (3.7)	1 (1.0)	3 (3.0)
Gastrointestinal disorders	**11 (20.4)**	**14 (14.0)**	**22 (22.0)**
Dry mouth	11 (20.4)	5 (5.0)	15 (15.0)
Abdominal pain upper	0 (0.0)	3 (3.0)	3 (3.0)
Nervous system disorders	**8 (14.8)**	**10 (10.0)**	**16 (16.0)**
Headache	6 (11.1)	9 (9.0)	14 (14.0)
Skin and subcutaneous tissue disorders	**3 (5.6)**	**14 (14.0)**	**15 (15.0)**
Eczema	1 (1.9)	4 (4.0)	5 (5.0)
Musculoskeletal and connective tissue disorders	**1 (1.9)**	**9 (9.0)**	**10 (10.0)**
Back pain	0 (0.0)	5 (5.0)	5 (5.0)
Injury, poisoning and procedural complications	**2 (3.7)**	**7 (7.0)**	**9 (9.0)**
Ligament sprain	1 (1.9)	2 (2.0)	3 (3.0)
Eye disorders	**2 (3.7)**	**5 (5.0)**	**7 (7.0)**
Dry eye	0 (0.0)	3 (3.0)	3 (3.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (1.9)**	**5 (5.0)**	**6 (6.0)**
Melanocytic naevus	1 (1.9)	2 (2.0)	3 (3.0)
Respiratory, thoracic and mediastinal disorders	**1 (1.9)**	**3 (3.0)**	**4 (4.0)**
Metabolism and nutrition disorders	**0 (0.0)**	**3 (3.0)**	**3 (3.0)**
Vascular disorders	**1 (1.9)**	**2 (2.0)**	**3 (3.0)**

[a] Percentages are based on the number of patients in each analysis group.
[b] Patients receiving placebo in Phase 3a are not included.
GPB=glycopyrronium bromide, SAFb=Safety Analysis Set (Phase 3b), TEAE=treatment-emergent adverse event.
Sorted by descending frequency in the 1% GPB overall group.

Dry mouth was the most frequent related TEAE, reported at an overall frequency of 17.2 % for GPB cream treated vs 4.8 % for the placebo treated in the placebo-controlled part (part a) of the pivotal phase 3 study and for GPB cream 1 % in phase 3 part b of six months follow up (Interim Analysis I) 11.4%, and 15.0% for 1 years follow-up (Interim Analysis II).

A questionnaire to assess anticholinergic effects was also used to in both studies with GPB cream. Most patients had no anticholinergic symptoms and only a few patients had mild anticholinergic symptoms throughout the placebo-controlled part of the pivotal phase 3 study. The only 2 reports of severe symptoms were 1 patient with dry mouth in the 1% GPB group at Day 15 with no evidence of dry mouth at Day 29 without changing the treatment and 1 patient with dry eyes in the placebo group. In the 6 months follow-up part of the study there were 14 patients with mild or moderate (1 patient) dry mouth, 6 of whom also had mild or moderate (1 patient) dry eyes. One of these patients also had blurred vision in addition to dry mouth and dry eyes. Mild dry eyes and in one case mild red eyes and mild drowsiness were observed in a total of 15 patients. For 2 patients each with drowsiness and concentration difficulties at week 12, this condition was already present at screening. During the 12 months follow-up a similar safety profile was shown.

The most common application site reaction was erythema. In the placebo-controlled part of the pivotal phase 3 study application site reactions such as erythema was reported in 5.7 % on GPB 1 % cream treated vs 4.8 % in placebo treated and application site papules in 2.3 % of GPB treated vs 0,0 in placebo treated. In Phase 3b, these reactions were more common during the initial 4 weeks with daily administration of GPB cream. Local tolerability at the application site was also assessed by the investigator using a skin reaction score. The vast majority of patients in both treatment groups (GPB cream 1 % and placebo) had a skin reaction score of 0 (i.e. no evidence of irritation) on both axillae at baseline, Day 15, and Day 29. In the phase 3 part b study, most patients (95 % - 97 %) showed no signs of irritation at the treated area between weeks 8 and 52.

Twelve SAEs in 11 patients were reported from the clinical studies. All were considered not drug-related except on case of unequal pupils with recovery. There were no deaths reported.

Table 15. Comparison of drug-related TEAEs in study Hyp1-18/2016, Phase 3a (SAFa), Phase 3b Interim Analysis I (SAFb) and Interim Analysis II (SAFb)

	Number (%)[a] of patients, 1% GPB		
System organ class Preferred term	**Phase 3a** **N=87**	**Phase 3b** **Interim Analysis I** **N=315**	**Phase 3b** **Interim Analysis II** **N=100**
Any drug-related TEAE	24 (27.6)	90 (28.6)	31 (31.0)
Gastrointestinal disorders	**15 (17.2)**	**38 (12.1)**	**15 (15.0)**
Dry mouth	14 (16.1)	36 (11.4)	15 (15.0)
Constipation	1 (1.1)	3 (1.0)	1 (1.0)
Abdominal distension	0 (0.0)	1 (0.3)	0 (0.0)
Lip dry	0 (0.0)	1 (0.3)	0 (0.0)
General disorders and administration site conditions	**7 (8.0)**	**37 (11.7)**	**14 (14.0)**
Application site erythema	4 (4.6)	14 (4.4)	8 (8.0)
Application site pruritus	1 (1.1)	7 (2.2)	3 (3.0)
Application site pain	1 (1.1)	6 (1.9)	2 (2.0)
Application site irritation	0 (0.0)	5 (1.6)	1 (1.0)
Application site dermatitis	1 (1.1)	3 (1.0)	1 (1.0)
Application site dryness	0 (0.0)	3 (1.0)	0 (0.0)
Application site papules	1 (1.1)	3 (1.0)	1 (1.0)
Application site rash	0 (0.0)	3 (1.0)	0 (0.0)
Application site swelling	0 (0.0)	2 (0.6)	0 (0.0)
Application site acne	0 (0.0)	1 (0.3)	0 (0.0)
Application site eczema	0 (0.0)	1 (0.3)	1 (1.0)
Chest pain	0 (0.0)	1 (0.3)	0 (0.0)
Mucosal dryness	0 (0.0)	1 (0.3)	0 (0.0)
Eye disorders	**4 (4.6)**	**17 (5.4)**	**6 (6.0)**
Dry eye	1 (1.1)	9 (2.9)	2 (2.0)
Ocular hyperemia	2 (2.3)	2 (0.6)	1 (1.0)
Pupils unequal	0 (0.0)	2 (0.6)	1 (1.0)
Vision blurred	0 (0.0)	2 (0.6)	0 (0.0)
Eye irritation	1 (1.1)	1 (0.3)	1 (1.0)
Eye pruritus	0 (0.0)	1 (0.3)	0 (0.0)
Visual impairment	0 (0.0)	1 (0.3)	1 (1.0)
Skin and subcutaneous tissue disorders	**1 (1.1)**	**13 (4.1)**	**2 (2.0)**
Dry skin	1 (1.1)	4 (1.3)	0 (0.0)
Eczema	0 (0.0)	2 (0.6)	0 (0.0)
Dermatitis atopic	0 (0.0)	1 (0.3)	1 (1.0)
Erythema	0 (0.0)	1 (0.3)	0 (0.0)
Hyperhidrosis	0 (0.0)	1 (0.3)	0 (0.0)
Parapsoriasis	0 (0.0)	1 (0.3)	0 (0.0)
Pruritus	0 (0.0)	1 (0.3)	0 (0.0)
Rash	0 (0.0)	1 (0.3)	0 (0.0)
Skin irritation	0 (0.0)	1 (0.3)	0 (0.0)

In general, the safety profile seems comparable in the short term and long-term perspective although the number of any TEAEs is increasing by week 28 and through week 52. If considering TEAEs evaluated as drug related there is only a slight increase in the number over time (please refer to table above).
In summary, the safety profile is dominated by adverse events in line with anticholinergic effects and of application site reactions. There are few SAEs and no deaths reported. To conclude, no serious systemic adverse events were reported in the submitted data that would indicate a new serious safety concern in adults at the proposed clinical use. The extent of exposure in adults presented in submitted data is considered satisfactory.

Some issues were requested for further clarification.
Based on the stated low systemic exposure to GPB when applying 1 % GPB cream, and that many of the adverse reactions in line with anticholinergic were observed in the facial area, the Applicant was requested to further discuss whether these reactions are most likely related to systemic exposure or whether it is a sign of misuse with facial contamination. The issue has been discussed by the Applicant. The ADR dry mouth may be partly due to contamination and partly due to systemic exposure and was observed as the most frequent ADR for oral administration of solution and tablets and for inhalative administration. Dry mouth was also reported when GPB was used as powder for palmar or plantar treatment of hyperhidrosis. However, in comparison with i.v., i.m. and orally administered formulations referred to by the applicant, exposure of the GP cream was considerably lower. Furthermore, a systemic adverse event such as e g urinary retention, has not been reported for GBP cream1 % cream (Interim Analysis I and II). It is therefore not unreasonable to assume that the facial including eye adverse events of suspected anticholinergic origin may at least partly be due to contamination. Although the mechanism of suspected anticholinergic adverse effects has not been fully elucidated the amendments in sections 4.2 and 4.4 that have been implemented in order to minimise the risk of contamination are considered sufficient. This includes the implemented request to amend and revise instructions on application in order to avoid contact of the cream with nose, eyes or mouth. The risk of misuse by applying the 1 % GPB cream on other areas of the body where sweating may occur, and the risk of potential overdose has been satisfactory described in section 4.9 of the SmPC.

Initially the suggested population to be treated would include children aged 12 years up to 18 years, However, the Applicant has in their response decided to exclude the paediatric population completely from the label until clinical data in the respective age group become available. Previous questions of the LoQ related to this population are therefore redundant and omitted.

From the perspective of the very common adverse reaction of dry mouth on a long-term basis and since reduced salivation can increase the risk of dental caries, the need of precautionary measures in the SmPC was requested. The SmPC has been amended with acceptable information about careful dental hygiene and dental health checks.
Furthermore, the presentation of data on TEAEs leading to discontinuation was not fully comprehensive. The Applicant has submitted adequate data. As these TEAEs s demonstrate a spread of different diagnoses with different time to event there is no specific pattern. The number is also limited, and no further action is considered necessary.
Supporting data was also requested supporting the SmPC section 4.8 labelling of Electrocardiogram QT prolongation in SOC Investigations, as uncommon, Furthermore, that the source of individual frequencies of the selected TEAEs stated in section 4.8 be discussed. The revised and updated section 4.8 including frequencies have been addressed more in detail in the submitted Annex 1 referred to by the Applicant. The proposed changes of 4.8 are acceptable.

Clinical safety issues raised by the CMSs involved in the procedure.
The CMS PT raised issues related to application on inflamed or irritated skin and this issue was also addressed by CMS ES from the perspective of potentially enhanced absorption in damaged skin as well as the use in patients with e. g., psoriasis inversa or psoriasis pustulosis generalisata. The SmPC

has been amended accordingly in section 4.4 with instructions that the product should be applied only on healthy skin. Furthermore, a clarification was requested by CMS PT concerning the classification of adverse reactions in section 4.8. This is considered solved.
The CMS ES requested that glaucoma should be listed in section 4.3 as a contraindication. This was supported by the RMS and in addition, taking into account other severe medical conditions that can be exacerbated by the anticholinergic effect of GBP cream apart from glaucoma such as paralytic ileus, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis and Sjögren syndrome, were as requested, added to section 4.3.
A special warning was requested by CMS ES about the risk of potential misuse/overdose by applying the product on other areas of the body where sweating may occur. An extensive paragraph is included in section 4.9 Overdose which is considered sufficient.

Conclusions on clinical safety
Glycopyrronium Cantabria (GPB 1 % cream) is applied topically to each armpit once a day the initial 4 weeks and thereafter twice a week, depending on the response to treatment. A number of glycopyrronium products, including parenteral, oral, or inhalational formulations are approved within EU and have been used for several years in various indications also in children and the safety profile is considered relatively well-known. The reported adverse events of Glycopyrronium Cantabria are in line with expected anticholinergic effects such as e.g. dry mouth, dry eye and furthermore local skin reactions, mainly erythema, were reported. No serious systemic adverse events that would indicate a new serious safety concern in adults at the proposed clinical use were reported in the submitted data. The extent of exposure in adults presented in submitted data is considered satisfactory. From a safety perspective there are in the RMS opinion no major concerns related to the adult population. Raised questions have been satisfactorily addressed.

Risk Management Plan
The MAH has submitted a risk management plan, 1.0 with data lock point 29 July 2020 and final sign-off 17 May 2022 in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmaco-vigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Glycopyrronium Cantabria.

Safety specification
Non-clinical
The Applicant has submitted a presentation of key findings of glycopyrronium from non-clinical studies/published literature concerning acute or repeat-dose toxicity studies, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance and other toxicity related information or data including safety pharmacology and discussed the relevance to human usage around these. Studies of genotoxicity, carcinogenicty, reproductive and developmental toxicit including separate safety pharmacology studies with GPB creams were not considered to add value and have not been performed.

Summary of conclusions by the applicant:

Single-and repeat dose toxicity
In the Phase 1b study (Hyp-02/2015), exposure with 1% cream was lower than exposure known from systemic administration of mentioned glycopyrronium-containing products and also compared to Qbrexza®, which is licensed for the topical treatment of primary axillary hyperhidrosis in the US: 1% GPB cream of [invented name] as a topical formulation is expected to be well-tolerated in humans.

Genotoxicity
There is no evidence of any genotoxicity of glycopyrronium from approved products.
Relevance to human usage: No genotoxicity is expected for 1% GPB cream of Sudormin.

Carcinogenicity
No indication for any systemic or local carcinogenic effect from glycopyrronium was observed. Thus, no carcinogenicity is expected for 1% GPB cream of Sudormin.

Reproductive and developmental toxicity
Pregnancy
There are no or limited amount of data from the use of GPB in pregnant women. Studies in animals have shown reproductive toxicity. Based on the low systemic exposure following dermal application of [Invented name], these findings are not considered relevant for human dermal use at the approved dosing. The use of [Invented name] may be considered during pregnancy, if necessary (SmPC, Section 4.6).

Breast-feeding
Glycopyrronium and its metabolites distributed into milk from lactating rats and generally reached higher concentrations in milk when compared with those observed in plasma (up to 11.3 times). However, systemic exposure of glycopyrronium following dermal application in patients is low and consequently, enriched concentrations in the milk would also still be low with no pharmacologic or toxicologic concern (SmPC, Section 5.3).
The contact of the suckling child with the cream or [Invented name]-treated skin should be avoided, therefore a decision must be made whether to discontinue breast-feeding or to discontinue [Invented name] therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman (SmPC, Section 4.6).

Use in pregnancy and lactation is included as missing information in this RMP.

Local tolerance
Local tolerability of GPB creams at concentrations of 0.5%, 1%, and 2% and as a 4% gel was assessed as part of the 7-day dermal local tolerance and toxicity study in minipigs. All tested concentrations and formulations were well tolerated and there were no adverse findings at the application sites. GPB 1% cream of Sudormin is expected to be well-tolerated in humans.

Other toxicityrelated information or data
Inadvertent dosing into the eyes is not expected to result in ocular irritation. Based on the very low potential of sensitization in mice, a sensitizing effect in humans cannot be completely ruled out in very rare cases. However, no indication of any skin sensitizing effect was observed so far from approved drug products or in clinical studies with GPB creams. No phototoxicity is expected by topical application of 1% GPB cream of Sudormin.

Safety pharmacology
Systemic exposure levels in dogs following inhaled administration of glycopyrronium doses that resulted in cardiovascular findings is expected to be 80- to 450-fold higher based on Cmax compared to systemic exposure levels detected in patients using the topically applied cream with 0.5%, 1% or 2% GPB. Thus, topical administration of 1% GPB cream of Sudormin is not expected to result in safety pharmacological effects in humans.

Clinical
The summary of safety concerns as presented by the Applicant can be seen in the table below.
Table SVIII.1: Summary of safety concern

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy and lactation

Missing information 1: Use in pregnancy and lactation
There are no or limited amount of data from the use of GPB in pregnant women. Studies in animals have shown reproductive toxicity (see Module SII, Table SII.1). Based on the low systemic exposure following dermal application of [Invented name], these findings are not considered relevant for human dermal use at the approved dosing. With regard to lactation, contact of the suckling child with the cream or [Invented name]-treated skin should be avoided.
Risk-benefit impact: Based on the low systemic exposure following the dermal application of [Invented name], the use of [Invented name] may be considered during pregnancy, if necessary.
The contact of the suckling child with the cream or [Invented name]-treated skin should be avoided, therefore a decision must be made whether to discontinue breast-feeding or to discontinue [Invented name] therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
Use in pregnancy and lactation will continue to be monitored through routine ongoing safety surveillance.

Assessor’s comment:The updated safety specification is acceptable.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant.

Plans for post-authorisation efficacy studies

Not applicable. There are no planned or ongoing post-authorization efficacy studies.

Assessor’s comment: The managing of the pharmacovigilance plan by routine pharmacovigilance as proposed by the Applicant is endorsed.

Risk minimisation measures (RMM)
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the Applicant.

Assessor’s comments: Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is generally endorsed.

Summary of activities in the risk management plan by medicinal product

Glycopyrronium Cantabria is authorized for the treatment of primary axillary hyperhidrosis in adults (see SmPC for the full indication).

It contains glycopyrronium bromide as the active substance and it is given by the topical route of administration.

Important risks of [invented name], together with measures to minimize such risks and the proposed studies for learning more about Glycopyrronium Cantabria's risks, are outlined below.

Summary of important risks

Missing information: use in pregnancy and lactation	
Risk minimization measures	Routine risk communication: SmPC, Sections 4.6, 5.3 PL, Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: medical prescription Additional risk minimization measures: none

Assessor's comments:
The updated summary of the medicinal product is acceptable.

Summary of the RMP

The submitted Risk Management Plan, version 1.0 with data lock point 29 July 2020 and signed-off 17 May 2022 is considered acceptable.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Axhidrox 2.2 mg/pump actuation cream, SE/H/2141/01/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Glycopyrronium Cantabria, 2,2 mg/ actuation, Cream is recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

Post approval commitments

Description	Due date
Additional ERA studies will be performed and submitted as a Type II variation.	Q2 2024
The Phase 3b part of study Hyp1-18/2016 is still ongoing.The results of the study should be submitted when finalised, as a post approval commitment in the form of a type II variation after completion of the MAA procedure.	Q4 2022

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Glycopyrronium Cantabria, 2,2 mg/ actuation, Cream was positively finalised on 2022-07-13.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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