30 May 2024
EMA/438224/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sialanar

International non-proprietary name: glycopyrronium

Procedure No. EMEA/H/C/003883/II/0029

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Steps taken for the assessment

Description	Planned date	Actual Date
Start of procedure	02 Mar 2024	02 Mar 2024
CHMP Rapporteur Assessment Report	26 Apr 2024	26 Apr 2024
CHMP Co-Rapporteur Assessment Report	26 Apr 2024	n/a
PRAC Rapporteur Assessment Report	03 May 2024	03 May 2024
CHMP Co-Rapporteur Assessment	07 May 2024	7 May 2024
PRAC members comments	07 May 2024	n/a
Updated PRAC Rapporteur Assessment Report	08 May 2024	n/a
PRAC endorsed relevant sections of the assessment report[3]	16 May 2024	16 May 2024
CHMP members comments	21 May 2024	21 May 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 May 2024	24 May 2024
RSI	30 May 2024	30 May 2024

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Proveca Pharma Limited submitted to the European Medicines Agency on 14 February 2024 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of children aged from 2 years and older for SIALANAR, based on the interim results from study PRO/GLY/005. This is a retrospective analysis of real world data from children aged under 3 years treated with glycopyrronium for severe drooling. As a consequence, sections 4.1, 4.2, and 4.4 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC. As part of the application the MAH is requesting a 1-year extension of the market protection.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0158/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0240/2014 was completed

The PDCO issued an opinion on compliance for the PIP, EMEA_C_001366-PIP01-12-M02.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. Please refer to the separate AR regarding one year additional market protection.

Scientific advice

The MAH did not seek Scientific advice at the CHMP for this variation.

2. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of children aged from 2 years and older for SIALANAR, based on the interim results from study PRO/GLY/005. This is a retrospective analysis of real-world data from children aged under 3 years treated with glycopyrronium for severe drooling. As a consequence, sections 4.1, 4.2, and 4.4 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC. As part of the application the MAH is requesting a 1-year extension of the market protection.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

3. Scientific discussion

3.1. Introduction

Sialorrhea or drooling is the unintentional loss of saliva from the mouth and is a normal phenomenon in infancy. Drooling is usually classed as normal in children up to 4 years of age. However, it is recognised that a proportion of children below 4 years of age suffer from severe sialorrhoea (chronic pathological drooling), usually associated with a chronic neurological condition. A substantial proportion of children with neurological disorders exhibit pathological drooling. The overall prevalence of significant chronic pathological drooling (sialorrhoea) in children is estimated at up to 0.6% (Fairhurst 2011). However, sialorrhoea is significantly more prevalent in neurologically impaired children, including those with cerebral palsy (CP), the most common motor disability of childhood. Estimates of the prevalence of sialorrhoea in these populations vary from 10% to 37%, but may be even higher in some subgroups, especially those with quadriplegic CP (Fairhurst 2011).

The current approved indication for Sialanar is "Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders."

The PIP granted for the PUMA is from 2 years and older. At the time of the initial PUMA there was insufficient information on the efficacy and safety of glycopyrronium to support use below 3 years of age. Since the launch of Sialanar new data have been published or generated by the Applicant to demonstrate the usage of glycopyrronium in children under 3 years of age, to support the efficacy, safety, dosage and duration of use in children from 2 years and older.

In terms of enteral anticholinergic treatment, glycopyrronium bromide (Sialanar) is the only treatment licensed throughout Europe for children from 3 to 17 years of age. Botulinum toxin A (BTX-A, Xeomin) is licensed for the symptomatic treatment of chronic sialorrhea due to neurological/neurodevelopmental disorders in children and adolescents aged 2 to 17 years and weighing ≥ 12 kg, however that is administered as an injection. Other drug treatments that are used for severe sialorrhoea include off-label treatment with glycopyrronium bromide, use of hyoscine patches and trihexyphenidyl.

Glycopyrronium bromide is a water-soluble synthetic quaternary amine. It is a peripheral antimuscarinic (anticholinergic) agent. GP acts as a competitive antagonist at muscarinic receptors in the autonomic nervous system.

The applied dose is based on the weight of the child, starting with approximately 12.8 micrograms/kg per dose (equivalent to 16 micrograms/kg per dose glycopyrronium bromide), three times per day and increasing by 12.8 micrograms/kg per dose every 7 days. Dose titration should be continued until efficacy is balanced with side effects and amended up or down as appropriate, to a maximum individual dose of 64 micrograms/kg body weight glycopyrronium or 6 ml (1.9 mg glycopyrronium, equivalent to 2.4 mg glycopyrronium bromide) three times a day, whichever is less.

The Applicant was granted a waiver by the EMA/PDCO ("Opinion of the Paediatric Committee on the acceptance of a modification of an agreed Paediatric Investigation Plan", EMA/PDCO/387731/2014) for the paediatric population from birth to less than two years on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset.

3.2. Non-clinical aspects

No new non-clinical data were provided. The submitted NCO does not indicate to which paediatric population the product is intended to. Although, weight of evidence for necessity of new non-clinical data according to ICH S11 was not provided, it is agreed on that no further published data are warranted. In general, non-clinical data are very sparse and safety aspects relies on a broad clinical data.

3.2.1. Environmental risk assessment

The Application comprises an extension of indication (Type II variation) for glycopyrronium bromide oral solution (Sialanar) and therefore requires an evaluation of the change in environmental exposure to conclude on the environmental risk of Sialanar presented in a corresponding environmental risk assessment (ERA) report.

The Applicant submitted an ERA report which provided a statement that "the extension of age range by one year, from children aged 3 years and older to children aged 2 years and older, will involve a very small additional number of children and very small total daily doses. As such, it will not impact the Environmental Risk Assessment."

Under the module 1.6, the applicant provided a study report (Report No. 37825) for the determination of the partition coefficient (n-octanol/water) of glycopyrronium bromide. The study was performed at the test facility Charles River Laboratories, UK, and included Good Laboratory Practice (GLP) compliance statement and a Quality Assurance statement. The analytical method (AP.225296.01) was fully validated, covering an assay range of 0.1-200 µg/mL for the quantitative determination of glycopyrronium bromide via HPLC-UV.

The partition coefficients were assessed in Milli-RO water, and in environmentally relevant buffer solutions of pH 4, pH 7, and pH 9. The mean Log D (distribution coefficient at a specific pH) for each n-octanol-buffer system was determined as follows:

Milli-RO water: Log D = -1.49 ± 0.18

pH 4 buffer: Log D = -1.32 ± 0.17

pH 7 buffer: Log D = -1.17 ± 0.21

pH 9 buffer: Log D = -1.09 ± 0.32

Glycopyrronium bromide was expected to be ionised at all tested pH values, therefore ion-corrected Log Kow values were not calculated. The pKa of glycopyrronium bromide is 11.53 and the unionised form will exist only under extreme pH conditions. The substance will be nearly 100 % ionised at all environmentally relevant pH values.

3.2.2. Discussion

The Applicant submitted an ERA report which provided solely a statement that the extension of indication will have no impact the environmental risk assessment. However, a simple statement without providing solid evidence for European disease prevalence data is not considered to be in accordance with the requirements outlined in the *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use* (EMEA/CHMP/SWP/4447/00 corr 2[1]*, 2006). The Applicant is requested to substantiate that a significant increase in environmental exposure is not expected for an additional paediatric population i.e., from 2 to 3 years of age. Therefore, an adequate risk assessment for Sialanar should be performed by providing an estimation of the predicted environmental concentration (PEC) of glycopyrronium bromide in surface water (PECsw) compartment based on

prevalence data, maximum dose per inhabitant per day and /or treatment regimen (**OC**).

To facilitate a screening for persistence, bioaccumulation and toxicity (PBT), the n-octanol-water/buffer partition coefficient has been determined. The study has been performed according to standard test protocol of OECD 107 in a GLP-certified test facility. The data is deemed reliable. Of note, the ion-corrected logarithmic octanol-water distribution coefficient for ionisable compounds (log Dow) for the neutral molecule could have been reported together with the respective dissociation constant (pKa) value(s). The ion-corrected Dow is equal to Kow. The Kow (ion corrected Dow) can be calculated as stated in the revised ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1, 2024). Despite a well-performed OECD 107 study, the Applicant does neither perform an assessment with regard to exceeding eventual trigger values, nor draws any conclusions with regard to the hazard assessment of Sialanar. The results from the determination of the n-octanol-water partition coefficient should be reported in an updated ERA report in the light of an adequate hazard assessment (**OC**).

3.2.3. Conclusion

The submitted ERA-report is not acceptable. Adequate PECsw calculation based on appropriate data together with the conclusion on the PBT screening needs to be compiled in a report that is considered according to the guidelines and provides a statement on the environmental risk assessment of glycopyrronium bromide/Salianar.

3.3. Clinical aspects

3.3.1. Introduction

The MAH is applying for a variation to the Sialanar indication with an extension of indication to include treatment of children aged from 2 years and older. The current approved indication for Sialanar is "Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders. "

The initial MAA was a paediatric-use marketing authorisation (PUMA) application with the legal basis of an article 10a of Directive 2001/83/EC (well-established use). The PIP granted for the PUMA is from 2 years and older. At the time of the initial PUMA there was insufficient information on the efficacy and safety of glycopyrronium to support use below 3 years of age.

To support this extension of indication, the MAH relies on existing pharmacokinetic data (Rautakorpi (1994)), a double-blind, placebo-controlled, randomised clinical trial conducted by the MAH (SALIVA study), a Cohort study (Papandreou et al. (2024)), Real World Data interim analysis (PRO/GLY/005) and Case series (Lovardi et al. (2022)).

GCP

The SALIVA study and Real-World Data interim analysis was performed in accordance with GCP as claimed by the MAH. The other studies are submitted as published literature. There is no statement about GCP compliance for the published studies. There are no statements about any GCP inspection.

3.3.2. Pharmacokinetics

The information on the pharmacokinetics of glycopyrronium bromide in children below 3 years was derived from a single dose study with IV administration reported in literature (Rautakorpi 1994). This study was also assessed in the initial PUMA.

Rautakorpi 1994 investigated the PK parameters of glycopyrronium bromide in 26 healthy children undergoing minor surgery. Patients were assigned to 1 of 3 groups: under 1 year of age (Group 1, n = 8), between 1 and 3 years of age (Group 2, n = 7), and over 3 years of age (Group 3, n = 11). Glycopyrronium bromide 5 micrograms/kg was given as a single intravenous (i.v.) injection before induction of general anaesthesia. Blood samples (for determination of drug concentrations in plasma) were collected just before and at 2, 4, 6, 10, 15, 30, 60, 120, 180, 240, 360, and 480 minutes after injection of glycopyrronium bromide.

PK parameters were determined using the following methods: For each subject, the terminal log-linear phases of the plasma GP concentration-time curves were identified visually. The elimination rate constant (λz) was determined by regression analysis of the log-linear part of the curve. The elimination half-life ($t_{½}$, z) was calculated from $t_{½}$, z = In2/ λ z. The areas under the GP concentration-time curves (AUC0-∞) were calculated using the linear trapezoidal rule as successive concentration values increased. The logarithmic trapezoidal rule was applied when successive concentration values decreased after the peak concentration value. AUC0-∞ was extrapolated to infinity by using the respective λ z value. Plasma clearance (Cl) and steady-state volume of distribution (Vss) of GP were calculated using noncompartmental methods based on statistical moment theory.

Absorption

No bioavailability data due to i.v administration.

Distribution and elimination

The plasma concentration after GP after a single IV injection are shown in figure 1.

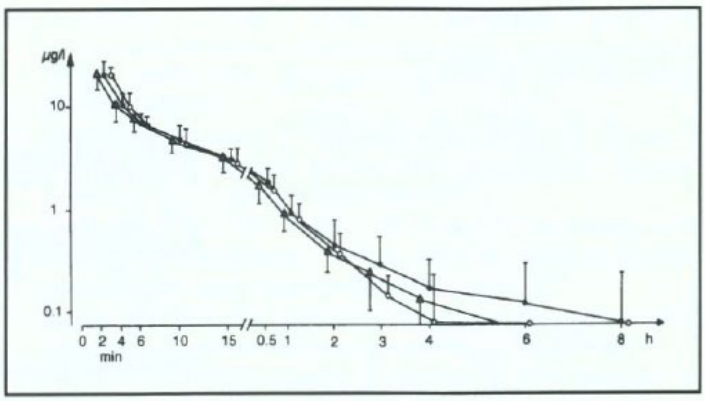


Figure 1. Plasma concentrations of glycopyrrolate after an intravenous injection (5 μg/kg). Note: Data are means ± SD. ●——● = patients under 1 year of age; ○——○ = patients between 1 and 3 years of age; ▲——▲ = patients over 3 years of age.

Modest changes in volume of distribution (Vss) and clearance (Cl) were observed in children between 1 and 3 years of age, leading to a statistically significant shorter elimination half-life (t½, z) than that observed in younger (<1 year of age) or older (>3 years of age) groups.

The youngest age group (< 1 year old; minimum age studied 0.19 years) was characterized by large interindividual differences. Both Vss and Cl varied by a factor of 6 in this group (Table 2). In the other paediatric age groups (Table 2), the variation was much smaller.

Table 2 PK characteristics by age group following single-dose i.v. glycopyrronium bromide (5 µg/kg)

	$AUC_{0-\infty}$ (µg.min/L)	$t_{½, z}$ (min)	Vss (L/kg)	Cl (L/h/kg)
Group 1 (age < 1 year)	297.4 (169.1 – 926.6)	129.5 (28.0 – 634.1)	1.83 (0.70 – 3.87)	1.01 (0.32 – 1.85)
Group 2 (age 1-3 years)	213.0 (134.9 – 308.8)	46.7 (43.3 – 74.1)	1.31 (0.80 – 1.71)	1.41 (0.97 – 2.22)
Group 3 (age > 3 years)	280.4 (167.5 – 488.8)	99.2 (39.2 – 371.3)	1.45 (0.76 – 3.56)	1.07 (0.61 – 1.79)

Data source: Rautakorpi, 1994

Key: AUC = area under the curve; Cl = clearance; $t_{½, z}$ = elimination half-life; Vss = distribution volume at steady state

Note: Data are means (ranges)

Dose proportionality and time dependencies

No data presented. The PK of GP was derived from a single dose study with one dose level only. Hence, no formal evaluation of the dose proportionality and time dependency of PK was performed.

Special populations

No data presented.

Pharmacokinetic interaction studies

No data presented.

Pharmacokinetics using human biomaterials

Not applicable.

3.3.3. Pharmacodynamics

No data presented. Evaluated in the initial PUMA, please refer to EPAR.

3.3.4. PK/PD modelling

No data presented.

3.3.5. Discussion on clinical pharmacology

The PK in children 2-3 years of age is based on data reported in publication Rautakorpi (1994), which investigated the PK parameters of glycopyrronium bromide in 26 healthy children following IV administration of the drug. Patients were distributed in 3 groups: under 1 year of age (Group 1, n = 8), between 1 and 3 years of age (Group 2, n = 7), and over 3 years of age (Group 3, n = 11).

The PK analysis methods stated to have been used seem to be acceptable, with the limitations of lack of detailed information pertaining to the literature data.

A shortened elimination half-life in children between 1 and 3 years of age was seen. However, the PK parameters were highly variable, and it is suggested that the PK parameters are comparable for all ages.

Whilst this is IV data and oral absorption is known to be slow and variable, it is agreed with the MAH that there is no physiological mechanism to support a difference in the pharmacokinetics of IV or oral glycopyrronium in children aged 2 to under 3 years compared to those aged 3 years and above.

The low and variable oral absorption defines the need for a slow titration phase based on the patient's weight as recommended in the SmPC.

3.3.6. Conclusions on clinical pharmacology

The pharmacokinetics of IV glycopyrronium in children aged 2 to under 3 years does not seem to differ from those aged 3 years and above, but only data from a single intravenous dose is submitted. The low and variable oral absorption defines the need for a slow titration phase based on the patient's weight as recommended in the SmPC.

3.4. Clinical efficacy

3.4.1. Dose response studies

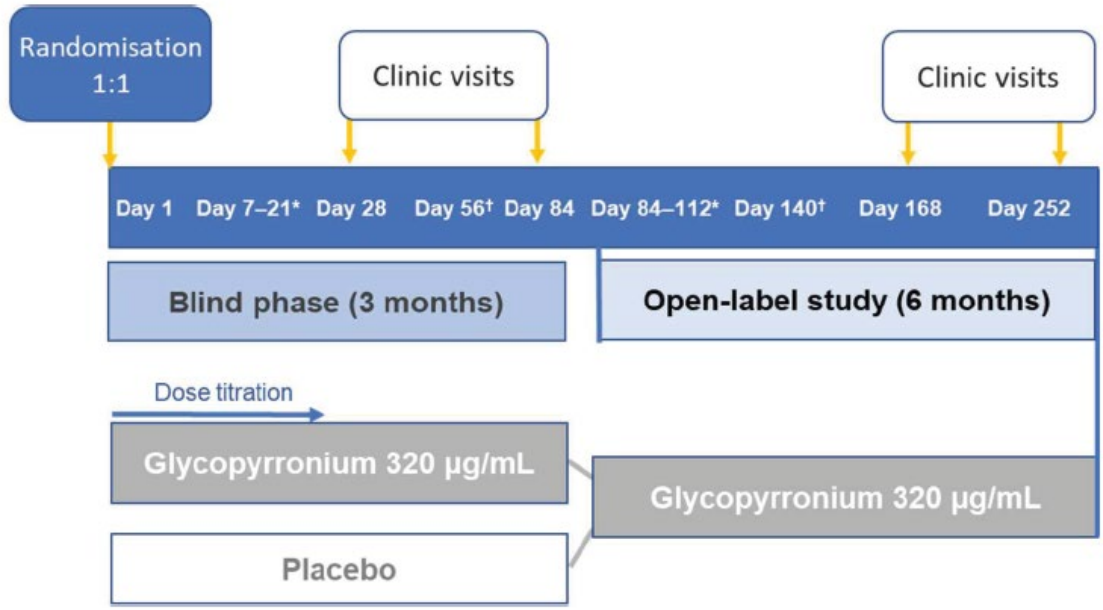
No dose response studies within the clinical efficacy data package were provided; instead analysis of clinical information relevant to dosing recommendation was presented. This is presented below for the individual studies.

3.4.2. Studies to support efficacy

To support efficacy in the extended target population, the MAH presented data from a double-blind, placebo-controlled, randomised clinical trial in children 3-17 years (SALIVA study), a Cohort study (Papandreou et al. (2024)), Real World Data interim analysis (PRO/GLY/005) and a case series (Lovardi et al. (2022)).

3.4.2.1. SALIVA Study: Double-blind, placebo-controlled, randomised clinical trial comparing the efficacy and safety of Sialanar® plus orAl rehabiLitation against placebo plus oral rehabilitation for chIldren and adolescents with seVere sialorrhoeA and neurodisabilities

Sialanar (320 µg/mL glycopyrronium) was compared to placebo in a 3-month, double-blind, randomized trial conducted in 13 French centres treating childhood neurodisabilities or in paediatric otorhinolaryngology centres. All patients who completed an initial 3-month blinded period were invited to receive 320 µg/mL glycopyrronium in a 6-month open-label study extension.



*Telephone interviews once a week. †Telephone interview.

Figure 1: Study design

Methods

Study participants

Key eligibility criteria included age between 3 and 17 years old, chronic neurodisabilities, severe sialorrhoea (defined as ≥6 on the modified Teachers Drooling Scale) and a Drooling Impact Scale (DIS) score ≥ 50 using the validated French edition of the DIS (DIS-F). All participants had received ≥3 months of non-pharmacological rehabilitation and continued to receive the same regimen throughout the trial.

Treatments

Oral solutions of Sialanar (320 µg/mL glycopyrronium) and placebo were administered in the blinded phase of the study. Sialanar oral solution was packaged and labelled compliant to clinical studies.

Objectives

Primary objective was to measure the efficacy of Sialanar used in addition to Standard of Care (SoC) compared with placebo plus SoC for the treatment of children with severe sialorrhoea related to chronic neurodisabilities in France.

Secondary objectives were to measure QoL of Sialanar used in addition to SoC compared with placebo plus SoC for the treatment of children with severe sialorrhoea in France and to assess the tolerability of sialanar used in addition to SoC for the treatment of children with severe sialorrhoea in France.

Outcomes/endpoints

The primary endpoint was the change in DIS-F score from baseline to day 84. The possible score ranges from 10 to 100, with the higher scores indicating greater severity and impact. The minimally clinically important difference was 13.6 points. DIS-F was completed at baseline, day 28 (±2 days) and day 84 (±5 days). Secondary efficacy endpoints included change in DIS between baseline and day 28, the proportion of responders (DIS improvement ≥ 13.6 points) at days 28 and 84, the proportion of good responders (DIS improvement ≥ 28 points) at day 84 and change from baseline in the number of used bibs or clothing over 7 days (DIS item 3) at days 28 and 84.

QoL endpoints included change from baseline to days 28 and 84 in DIS item 9 ('To what extent did your child's drooling affect his or her life?') and in DIS item 10 ('To what extent did your child's dribbling affect you and your family's life?'). For tolerability, the parent/carer was instructed to complete a notebook daily to record any adverse events. Adverse events were collected from the first dose of study treatment and are presented during the titration period (day 0–28), during the maintenance phase (day 29–84), and overall.

Assessors comment

The primary objective was to measure the efficacy of Sialanar compared with placebo for the treatment of children with severe sialorrhoea related to chronic neurodisabilities.

Secondary objectives were to measure QoL of Sialanar compared with placebo plus SoC for the treatment of children with severe sialorrhoea and to assess the tolerability of sialanar.

The doses and titration used in the study was the same as recommended in the Sialanar SmPC. Overall, the study objectives and treatments are acceptable.

The SALIVA study did not include the age group (children aged 2-3 years) applied for in this extension of indication variation. The MAH states that the study can be used to compare efficacy data for children aged 2-3 years. In the SALIVA study the primary endpoint was the change in the validated French edition of the Drooling Impact Scale (DIS-F) score from baseline to day 84. The possible score ranges from 10 to 100, with the higher scores indicating greater severity and impact. The minimally clinically important difference was 13.6 points. Overall, the DIS-F endpoint is considered acceptable as it is a validated tool and the clinically important difference of 13.6 points is considered adequate as similar clinically important differences is used in the literature e.g. Reid 2019. The supportive Cohort study and case series, including children below 3 years of age, (Papandreou et al. 2024 and Lovardi et al. 2022) used the DIS score. The MAH is asked to discuss the differences between the DIS and DIS-F score and justify that the endpoints can be compared between the studies. **(OC)**

In the initial PUMA the main studies (Zeller 2012a and Mier et al 2010) used the modified 9-point Teacher's Drooling Scale (mTDS) as primary endpoint and therefore it is difficult to compare the new published studies with the studies from the initial PUMA.

Sample size

For the SALIVA study, DIS-F score at D84, with a standard deviation of 13.63 [Reid, 2010] is the primary outcome. As clinically minimal important difference, a difference of 13.6 points in mean score

between groups, is suggested. With 90% power and a type 1 error rate of 5% a number of 23 patients in each group, is required.

Allowing for approximately 20-30% loss to follow up, a total number of 60 children is estimated to be included in the study, to evaluate the primary efficacy endpoint.

This number of patients to be enrolled in the study, is further extended with 30% to a total of 80 patients. This, to ensure enough patients to continue for the OLSE part of the study (for assessment of safety).

Randomisation and blinding (masking)

Patients enrolled in the study, are randomised to receive the study drug in a double-blind fashion, either Sialanar or placebo, and in a 1:1 ratio into the two treatment arms.

After approval to participate in the OLSE phase, unblinding of study medication is done. For the other patients refusing to participate in the OLSE study, the unblinding is planned after D84 timepoints for all patients, are reached.

Assessors comment:

Sample size determination and randomisation/blinding for the study can be endorsed.

Statistical methods

Analysis sets:

The full analysis data set is defined according to the intention-to-treat (ITT) principle. ITT population includes all patients randomised for the double-blind phase. This population is used for the primary analysis.

The modified intention-to-treat (mITT) analysis data set excludes all patients who will be deemed ineligible after randomisation or who will never start the study medication.

Per-protocol (PP) analysis data set is the subset of the ITT data set, of patients receiving at least one dose of randomised therapy and without major protocol violations or deviations, that would interfere with the analysis of the endpoints.

Open Label Study Extension (OLSE) analysis data set consists of all patients accepting to participate in the study extension and receive at least one dose of Sialanar in the OLSE phase. Patients will be analysed according to the treatment and overall:

- Ex-sialanar arm: Patients who continue the treatment After D84 corresponding to month 3 to 9 of treatment with sialanar;
- Ex-placebo arm: Patients who start sialanar start after D84, corresponding to the first 6 months of treatment with the product.

For the primary efficacy analysis, the change in DIS score between baseline D0 and D84 is assessed. This is done by assessing the mean difference in DIS score between D0 and D84 (+/- 5 days), comparing it between the two treatments arms (sialanar and placebo). The mean DIS score is calculated at D0 and D84 in each treatment arm. Difference between the two timepoints scores are calculated for each patient, then the mean of patients' score differences are provided in each arm.

The mean change in scores on the DIS in the sialanar arm is compared to the placebo arm based on a univariate analysis using Student t-test (equality of variances is tested by the Levene test and test of normality will be done from the appearance of histograms, and if necessary – from result of the Shapiro-Wilk test). In case unequal variances appear, the Satterthwaite approximation method is preferred). The statistical test will be two-sided and the significance level 5%. A 13.6 point change is considered as a minimal clinically relevant change.

However according to the section "Changes in Planned Analyses" in the CSR p. 49, changes have been done compared to what was described in the last protocol and SAP. For the univariate comparative methods, the non-parametric Wilcoxon-Man-Whitney test was used instead of the student's t-test to statistically compare quantitative endpoints (e.g. change in score) between the treatment groups, as normality of scores and change score was not met.

Sensitivity analyses as comparison analyses are done based on the PP analysis data set and other data, to evaluate missing data.

Regarding missing data, the analyses will be based on available data ("observed-case analysis"), considering missing data as noninformative. No imputations of values for missing data is performed, unless specified otherwise. For the primary analysis, DIS scores unavailable at D84 are (because of reasons such as early termination, lost to follow-up etc.), are considered non-responder (the D0 replace the D84 measurement).

Rapporteur's comment:

Statistical Methods

For the primary analysis, FAS is being used, defined according to the ITT principle (all patients randomised are included). This is correct and endorsed.

According to the SAP mean change in DIS-F scores between D0 and D84, are compared, based on a univariate analysis is used as the primary analysis, using Student t-test. Based on Levene test, equality of variances is tested. Whether data is normality distributed, is assessed, based on a visual assessment of histograms, and if necessary, based on a Shapiro-Wilk test.

Changes to the last protocol version and SAP stated in the section "Changes in Planning Analysis", p. 49, related to the univariate comparative methods, that the non-parametric Wilcoxon-Man-Whitney test was used instead of the student's t-test to statistically compare the quantitative endpoints such as change in score between treatment groups, as assumption of normality was not met, is appropriate and endorsed.

Analyses are based on data available – and missing data are considered non-informative.
For the primary analysis missing data at D84 are considered non-responders, when reason such as early termination appears. This is endorsed. Total numbers of patients in the two arms in the analysis dataset are balanced.

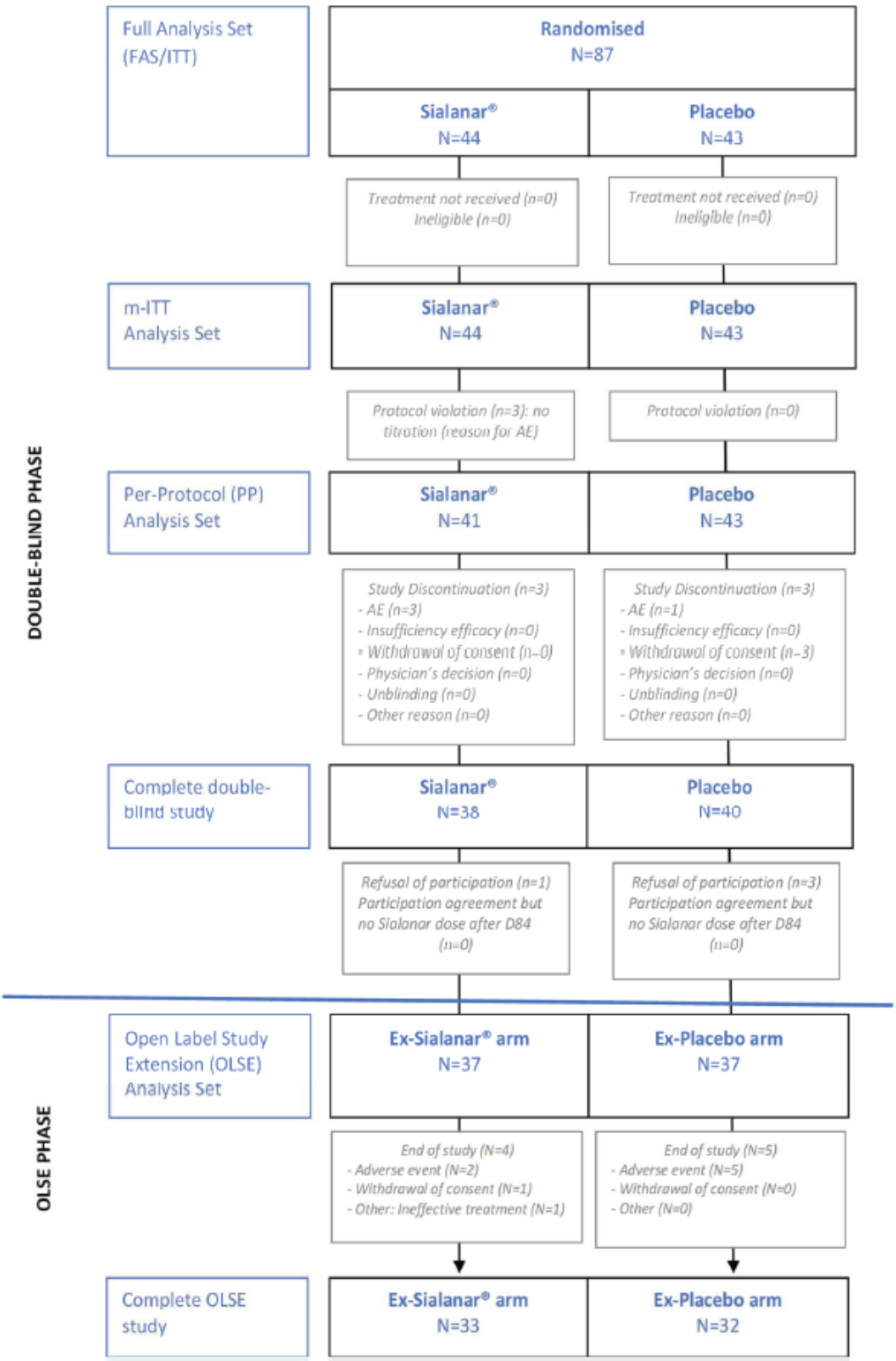
It is considered that sufficient sensitivity analyses are conducted e.g. based on PP analysis data set, to compare.

Sensitivity analyses performed seems appropriate.

For the observational studies being compared to the result of the current study, means are presented. MAH is requested to clarify the potential impact of comparing median to means from the studies, when comparing results. **(OC)**

Results

Participant flow



Recruitment

This was a multicentre clinical study conducted at 13 sites in France. First patient was enrolled on 3 June 2021 and last patient completed on 16 May 2023.

Conduct of the study

The study was conducted according to Good Clinical Practice guidelines and in full compliance with the World Assembly Declaration of Helsinki and its most recent amendments. The protocol was modified three times after the first authorisation of the Ethics Committee to extend the inclusion period, clarification on study procedure in the OLSE and changes in the duration of the study (from 18 month to 24 month) due to extension enrolment period.

Baseline data

Table 5. SALIVA Demographics

		320 µg/mL glycopyrronium *n* = 44	**Placebo *n* = 43**
	Female sex, *n* (%)	17 (38.6)	25 (58.1)
	Median (Q1, Q3) age, years:months	9:11 (7:7, 14:8)	10:2 (7:4, 14:7)
	Median (Q1, Q3) weight, kg	27.6 (18.4, 36.0)	25.0 (20.0, 40.5)
Neurodisability, *n* (%)	Cerebral palsy	19 (43.2)	24 (55.8)
	Epilepsy	14 (31.8)	14 (32.6)
	Intellectual disability	12 (27.3)	14 (32.6)
Modified Teacher's Drooling Score, *n* (%)	6, Severe: drools to the extent that clothing becomes damp; occasionally	2 (4.5)	1 (2.3)
	7, Severe: drools to the extent that clothing becomes damp; frequently	4 (9.1)	3 (7.0)
	8, Profuse: clothing, hands, tray, and objects become wet; occasionally	6 (13.6)	4 (9.3)
	9, Profuse: clothing, hands, tray, and objects become wet; frequently	32 (72.7)	35 (81.4)

Numbers analysed

In total, 88 children were enrolled, and of these, 87 were randomized and included in the full analysis set and modified intention-to-treat populations (mITT).

Outcomes and estimation

Primary endpoint

For the primary endpoint, the median (Q1, Q3) change in total DIS score from baseline to day 84 was significantly greater (improvement) with 320 mcg/mL glycopyrronium than placebo (−29.5 [−44.5, 0] vs −1 [−16, 5]; $p < 0.001$) (Table 6). Similar results were obtained in all sensitivity analyses, including the analysis of only patients with a DIS completed strictly by the same person at days 0 and

84 (320 µg/mL glycopyrronium [n = 42] vs placebo [n = 40]: −29.5 [−44.0, 0] vs 0 [−14, 5.5]; p < 0.001). The median change in total DIS score from baseline to day 84 was statistically different within the two groups (p < 0.001 for 320 mcg/mL glycopyrronium and p = 0.01 for placebo).

Secondary endpoints

Improvements in total DIS score were noted early after initiation, with a significant difference observed between 320 mcg/mL glycopyrronium and placebo at day 28 (−25 [−43, −0.5] vs −2 [−21, 1]; p < 0.01). There were significantly more responders (based on minimally clinically important difference) and good responders with 320 mcg/mL glycopyrronium versus placebo at day 28 (61.4% and 45.5% vs 27.9% and 18.6%, both p < 0.01) and at day 84 (63.6% and 52.3% vs 34.9% and 16.3%, both p < 0.01). The difference was also significant when adjusted for baseline DIS (p < 0.01).

Table 6. Primary and secondary efficacy analysis

DIS score[a]		320 µg/mL glycopyrronium n=44	Placebo n=43	P value[b]
Total DIS score				
Baseline	Median (Q1, Q3)	66.5 (60, 79)	70 (63, 82)	—
Day 28	Median (Q1, Q3)	43 (22.5, 65.5)	65 (48, 79)	—
	Median change from baseline (Q1, Q3)	−25 (−43, −0.5)	−2 (−21, 1)	<0.01
	95% CI	−37 to −6	−9 to 0	<0.01
	p[c]	<0.001	<0.01	
	Responders[d], n (%)	27 (61.4)	12 (27.9)	
	95% CI	43–79.8	2.5–53.3	<0.01
	Good responders[e], n (%)	20 (45.5)	8 (18.6)	
	95% CI	23.7–67.3	0–45.6	
Day 84	Median (Q1, Q3)	40 (22, 62.5)	66 (51, 85)	—
Primary efficacy endpoint:	Median change from baseline (Q1, Q3)	−29.5 (−44.5, 0)	−1 (−16, 5)	<0.001
	95% CI	−37 to −8	−13 to 0	
	p[c]	<0.001	0.01	
	Responders[d], *n* (%)	28 (63.6)	15 (34.9)	<0.01
	95% CI	46–81.6	10.8–59	
	Good responderse, n (%)	23 (52.3)	7 (16.3)	<0.001
	95% CI	31.9–72.7	0–43.7	
DIS item 3 score: number of used bibs/clothes per day				
Baseline	Median (Q1, Q3)	6 (4, 7.5)	5 (4, 8)	—
Day 28	Median (Q1, Q3)	3 (1, 4.5)	4 (3, 6)	—
	Median change from baseline (Q1, Q3)	−1.5 (−4, 0)	0 (−2, 0)	0.02
	95% CI	−3 to 0	−1 to 0	
	p[c]	<0.001	0.032	
Day 84	Median (Q1, Q3)	3 (1, 5)	5 (3, 9)	—
	Median change from baseline (Q1, Q3)	−2 (−4, 0)	0 (−1, 0)	<0.01
	95% CI	−3 to 0	−1 to 0	
	p [c]	<0.001	0.34	

[a]Higher scores indicate greater severity and impact.
[b]Mann–Whitney U test (score change) or X2 test (responder analysis).
[c]Wilcoxon signed-rank test (paired comparison).
[d]DIS improvement ≥ 13.6 points.
[e]DIS improvement ≥ 28 points.
Abbreviations: CI, confidence interval; DIS, Drooling Impact Scale; Q1, Q3, quartile 1, quartile 3.

QoL endpoints

In terms of measures related to Quality of Life (QoL), there was a significantly greater reduction in DIS item 3 with 320mcg/mL glycopyrronium versus placebo: the median (Q1, Q3) number of bibs/clothes used per day with 320 mcg/mL glycopyrronium versus placebo was −1.5 (−4, 0) versus 0 (−2, 0) (p = 0.02) at day 28 and − 2 (−4, 0) versus 0 (−1, 0) (p < 0.01) at day 84. Improvements were also observed with 320 mcg/mL glycopyrronium in the DIS item related to the child's QoL ('To what extent did your child's drooling affect his or her life?'), with 3-point reductions (−5, 0) at day 28 (vs 0 [−2, 0] with placebo; p < 0.01) and day 84 (vs 0 [−3, 0] with placebo; p = 0.01) from a median score of 8 at

baseline in both treatment arms (Table 7). For the QoL item related to the extent that the child's dribbling affected the family's life, treatment with 320 mcg/mL glycopyrronium reduced the median score of 9 at baseline by 2 points (−6.5, 0) at day 28 (vs −1 [−3, 0] with placebo; p = 0.03) and by 2.5 (−7, 0) points at day 84 (vs 0 [−2, 0] with placebo; p < 0.01).

Table 7. DIS Quality of Life analysis

	320 µg/mL glycopyrronium	Placebo	pc
DIS item 9 score: to what extent did your child's drooling affect his or her life?[a]			
	n = 44	*n* = 43	
Median (Q1, Q3) score at baseline	8 (5, 10)	8 (5, 10)	—
Change from baseline to day 28	−3 (−5, 0)	0 (−2, 0)	<0.01
Change from baseline to day 84	−3 (−5, 0)	0 (−3, 0)	0.01
DIS item 10 score: To what extent did your child's dribbling affect you and your family's life?[a]			
	n = 44	*n* = 43	
Median (Q1, Q3) score at baseline	9 (7.5, 10)	9 (7, 10)	—
Change from baseline to day 28	−2 (−6.5, 0)	−1 (−3, 0)	0.03
Change from baseline to day 84	−2.5 (−7, 0)	0 (−2, 0)	<0.01

[a]Higher scores indicate greater severity and impact.

Long-term efficacy

Long term efficacy was assessed in the OLSE of the SALIVA study. The median change in DIS score from D84 to D252 was assessed in the ex-Sialanar® group who continued Sialanar® after the blind period and in the ex-placebo group who initiated the treatment at D84. In the ex-Sialanar® group the patients continued to respond, the median change in DIS score from D84 to D252 was -2 (IQR -12; 0) and was statistically different between the two measurements for the group (p=0.0045). In total, 8 additional patients (21.6%) became responders to treatment during the OLSE period in the ex Sialanar group. In the ex-placebo group, the median change in DIS score from D84 to D252 was -18 (IQR -44; -5) and was statistically different between the two measurements for the group (p<0.0001). In total, 22 (59.5%) and 14 (37.8%) patients became responders and good responders to treatment during the OLSE period, respectively in the ex-placebo group.

Dosing data

The SALIVA study shows that the mean initial volume of 320 mcg/ml glycopyrronium (equivalent to 400mcg/ml glycopyrronium bromide) was 1.1ml (440mcg) (range 0.6 – 2 ml or 240 – 800mcg) with a mean maintenance dose of 4.5ml (1,800mcg) (range 1.2 – 6ml or 480 – 2,400 mcg)) at day 84. The initial dose equates to the first dose titration level as per the SmPC with patients being titrated according to the titration schedule to balance efficacy with tolerability. The mean dose at Day 28 was 4ml (160 mcg/dose) ranging from 1.2 to 6ml (480 to 2,400 mcg/dose) in line with the dose titration in the Sialanar SmPC. From the dosage range it can be seen that downward titration occurred as well as upward titration, in line with the known usage of glycopyrronium for treatment of chronic drooling.

Assessors comment

In total, 88 children were enrolled, and of these, 87 were randomized and included in the full analysis set and modified intention-to-treat populations (mITT).

The most common cause for sialorrhea in the Sialanar group was cerebral palsy (43.2%), followed epilepsy (31.8%) and intellectual disability (27.3%).

A significant change at D84 from baseline was seen for the primary endpoint with Sialanar compared to Placebo [Q1, Q3]; (−29.5 [−44.5, 0] vs −1 [−16, 5]; p < 0.001). The change for the Sialanar treatment arm is considered clinically relevant. The same clinically relevant change was seen for the secondary endpoint at D28 (−25 [−43, −0.5] vs −2 [−21, 1]; p < 0.01).

There were significantly more responders (based on minimally clinically important difference) and good responders with Sialanar versus placebo at day 28 (61.4% and 45.5% vs 27.9% and 18.6%, both p < 0.01) and at day 84 (63.6% and 52.3% vs 34.9% and 16.3%, both p < 0.01).

In terms of measures related to Quality of Life, the median (Q1, Q3) number of bibs/clothes used per day with Sialanar versus placebo was −1.5 (−4, 0) versus 0 (−2, 0) (p = 0.02) at day 28 and − 2 (−4, 0) versus 0 (−1, 0) (p < 0.01) at day 84. Improvements were also observed with Sialanar in the other QoL endpoints.

With regard to long term efficacy, the median change in DIS score from D84 to D252 was assessed in the ex-Sialanar group who continued Sialanar after the blind period and in the ex-placebo group who initiated the treatment at D84. In the ex-Sialanar group the patients continued to respond, the median change in DIS score from D84 to D252 was -2 (IQR -12; 0) and was statistically different between the two measurements for the group (p=0.0045). In the ex-placebo group, the median change in DIS score from D84 to D252 was -18 (IQR -44; -5) and was statistically different between the two measurements for the group (p<0.0001).

Overall, the study supports the efficacy and long-term of Sialanar for children and adolescents aged 3 years and older with chronic neurological disorders. The study may be used to compare efficacy with the following studies including children 2-3 years of age, with the known limitations of comparing outcomes between trials.

The MAH is requested to provide number of children at the different ages (3 years old, 4 years old etc.) to see how many children in the lower ages were included in the trial **(OC)**

3.4.2.2. Papandreou et al. (2024): Comparative Efficacy and Side Effect Profiles of Interventions for Pediatric Saliva Control: A Cohort Study

Papandreou et al. (2024) conducted a cohort study of children referred to a specialty Saliva Control service between May 2014 and November 2019, using quantitative data from pretreatment and post-treatment questionnaires (the Drooling Impact Scale [DIS], Drooling Rating Scale [DRS]) and recording of side effects.

Methods

Study participants

Patients under the age of 18 years with saliva control issues referred to a specialist pediatric multidisciplinary saliva control service.

Treatments

Patients were offered conservative management, followed sequentially when appropriate by targeted cognitive behavioral (orofacial myofunctional) therapy, oral and/or inhaled anticholinergics, injections of low-dose botulinum toxin A (Botox; onabotulinumtoxinA, Allergan; BTX-A) to bilateral submandibular and unilateral parotid saliva glands, and onward referral to the specialist surgical services for submandibular duct transposition.

The clinical choice of which enterally administered anticholinergics to use as first line was based on the presence or absence of dyskinesia. Children whose saliva control difficulties were associated with an underlying dyskinetic movement disorder were placed on trihexyphenidyl initially and those without dyskinesia on glycopyrronium bromide.

The dose for Glycopyrronium Bromide was as follow:

- Start 0.25mg if less than 15kg, 0.5mg if 15-25kg and 1mg if >25kg; once daily
- Slow incremental doses, every 1-2 weeks to twice daily then three times a day.
- Further increases up to maximum of 0.04mg/kg per dose, three times a day

Objectives

To compare efficacy and side effect profile data on conservative, behavioral, pharmacological, and surgical treatments used for pediatric saliva control.

Outcomes/endpoints

Full medical, swallowing, communication and dental history, Drooling Impact Scale (DIS) and Drooling Rating Scale (DRS) were obtained, both before interventions and every 3 months afterwards, with a minimum follow-up time of 12 months (range, 12.5-102 months). Relevant downstream results correspond with score changes at 3 months after each new intervention (eg, medication change or toxin injection).

These last 2 subscales in DIS represent an important subcomposite for the impact of drooling on everyday life for the individual and family. When using the DIS, the strength of benefit or effect size is set out for changes observed after intervention. A minimal clinically important of difference in the score of >10 is reported as reliable, a score of 20-28 a good outcome, and a score of >28-38 being very good to excellent.

Finally, caregivers were instructed to report any side effects to the clinical care team whenever these occurred and also specifically asked for their presence or absence in each follow-up appointment.

Assessors comment

The study was a single center cohort study. The objective was to compare efficacy and side effect profile data on conservative, behavioral, pharmacological, and surgical treatments used for pediatric saliva control. The study included patients under 18 years, including patients in the age-group 2-3 years as applied for in this extension of indication variation.

Patients were offered different treatment, including weight-based Glycopyrronium Bromide in a different dose-range than in the SALIVA study.

The treatment used was enteral glycopyrronium bromide, not further detailed in the study. The MAH is asked to justify that the composition and release characteristics of the marketed product Sialanar are sufficiently similar to the products used in this study. **(OC)**

One of the endpoints were DIS before interventions and every 3 months afterwards, with a minimum follow-up time of 12 months. A minimal clinically important of difference in the score of >10 was reported as reliable, a score of 20-28 a good outcome, and a score of >28-38 being very good to excellent.

There are several limitations to the study design; Specific inclusion and exclusion criteria are not mentioned, the dose-ranges differ from the dose-ranges in the Sialanar SmPC and SALIVA study and patients were not randomized and blinded.

Sample size

NA

Randomisation and blinding (masking)

NA

Statistical methods

Descriptive statistics were used to summarize key components of the data set.

To compare pre-therapy and post-therapy (DIS, DRS and Impact of Drooling) values, one-way ANOVA was applied. Bonferroni correction for multiple comparisons was used, when appropriate. A P-value of 0.05 was considered statistically significant.

Assessors comment

Statistical methods used for this study are appropriate.

Results

Participant flow

Not available.

Recruitment

A cohort study was performed, examining patients under the age of 18 years with saliva control issues referred to a specialist paediatric multidisciplinary saliva control service (serving a total population of around 8 million) between May 2014 and November 2019. The end date for the study was defined by the coronavirus disease-2019 pandemic from early 2020 onward. Clinical follow-up of this cohort every 3 months has continued to date, after the initial referral and intervention in this time frame.

Conduct of the study

This study was considered as a service evaluation by the Health Research Authority and by the GSTT Trust audit and clinical governance department. Because there was no change in clinical practice while

collating the information on the database and data were anonymized upon collection, no specific ethical approval was deemed to be required.

Baseline data

Table I. Study cohort characteristics

Primary diagnoses	No. of participants (%)/483	Sex, male:female (232:193)	Age, years, mean (range)
Cerebral palsy*	234 (48.4)	127:107	7.4 (1.8-16.3)
Worster-Drought syndrome	29 (6.0)	21 : 8	9.6 (6.2-14.7)
Autistic spectrum disorder	33 (6.8)	24:9	8.8 (5.1-15.9)
Progressive neurometabolic conditions (eg, Tay Sachs, n = 3; Battens, n = 5; mitochondrial, n = 3)	39 (8.1)	18:21	4.6 (1.9-18.8)
Other genetic/syndromic conditions (eg, Rett, n = 9; Lesch-Nyhan, n = 6)	86 (17.8)	39:47	10.1 (5.5-19.2)
Epileptic encephalopathy	19 (3.9)	10:9	9.2 (4.0-17.5)
Other post brain injury (inflammatory/infective/trauma/tumor)	14 (2.9)	7:7	6.1 (2.5-12.4)
Speech delay/isolated sialorrhoea	29 (6.0)	16:13	8.9 (4.4-15.2)

Reported ages reflect the time of initial assessment.
*In our cerebral palsy cohort, most patients were of GMFCS levels of IV-V (224/234 [95.7%]), whereas the minority (10/234 [4.3%]) of GMFCS levels I-III.

Numbers analysed

In total, 483 children and young people (262 males, 221 females; age range, 20 months to 19 years) were seen in the South Thames Regional Saliva Control Clinic based at the Evelina London Children's Hospital (Table I) within the specified time period**.**

Outcomes and estimation

The comparative outcomes of the given therapies are shown in Table 2. The authors demonstrated that medical intervention with enteral anticholinergic treatments was used for children with more significant drooling. Glycopyrronium was shown to be effective with a change in DIS of 21.54 and DRS 0.82 and a difference in Drooling Impact on the child and family of 2.55 (range 2.14 to 2.95).

Table II. Comparative outcomes of interventions

Interventions	Myofunctional therapy (n = 9)		Ipratropium bromide (n = 80)		Glycopyrronium bromide (n = 150)		Trihexyphenidyl (n = 87)		BTX-A (n = 207; total courses = 551)		Surgery (n = 31)	
Average DIS preintervention	37.83		55.8		57.33		58.57		65.97		57.78	
Difference in score, before and after intervention	**Mean (95% CI)**	**SE**	**Mean (95% CI)**	**SE**	**Mean (95% CI)**	**SE**	**Mean (95% CI)**	**SE**	**Mean (95% CI)**	**SE**	**Mean (95% CI)**	**SE**
Difference DIS/100	**13.00 (8.17-21.83)**	**3.48**	**11.11 (8.88-13.35)**	**1.13**	**21.54 (19.07-24.02)**	**1.25**	**22.37 (18.93-25.81)**	**1.73**	**32.47 (29.24-35.70)**	**1.64**	**29.03 (22.34-35.73)**	**3.27**
Difference DRS Severity/5	0.33 (0.21-0.66)	0.22	0.70 (0.52-0.89)	0.09	1.08 (0.93-1.23)	0.08	1.11 (0.89-1.33)	0.11	1.67 (1.51-1.83)	0.08	1.48 (1.17-1.80)	0.15
Difference DRS Frequency/4	0.67 (0.34-0.99)	0.17	0.28 (0.14-0.42)	0.07	0.82 (0.69-0.95)	0.06	0.87 (0.71-1.03)	0.08	1.38 (1.25-1.50)	0.06	1.16 (0.86-1.46)	0.15
Difference Impact of Drooling on individual and family/10	1.78 (0.81-2.75)	0.49	1.44 (0.95-1.93)	0.25	2.55 (2.14-2.95)	0.21	2.52 (1.94-3.09)	0.29	3.76 (3.30-4.21)	0.23	4.00 (2.95-5.05)	0.51

Dosage data

Not available.

Assessors comment

In total, 483 children and adolescents (age range, 20 months to 19 years) were included in the study by Papandreou et al.

The most common cause for sialorrhea in the cohort was cerebral palsy (48.4%), followed by genetic or syndromic conditions (17.8%) and progressive neurometabolic conditions (8.1%).

150 of the included children and adolescents were treated with glycopyronium bromide. From the data given in the article it cannot be concluded how many children that was included in the age-group 2-3 years and further it cannot be concluded, if any of the children aged 2-3 years were treated with glycopyronium bromide. This is a crucial limitation for this study with regard to supporting the efficacy in children aged 2-3 years. The MAH is asked to justify that this study can be used to support the efficacy and use of glycopyronium bromide in children aged 2-3 years. **(MO)**

With regard to the efficacy of glycopyrronium bromide in the study, a mean change in DIS (95% CI) of 21.54 (19.7-24.81) was reported. This is similar to the reported median change of −29.5 on the DIS-F in the SALIVA study. However, from the data provided in this cohort study it is difficult to compare the efficacy of glycopyrronium bromide in children aged 2-3 years with to the SALIVA study due to the missing details on age range in the glycopyrronium bromide group.

3.4.2.3. PRO/GLY/005: Retrospective analysis of real-world evidence on the use of glycopyrronium bromide in children under 3 years of age with sialorrhea

Interim analysis from a retrospective observational cohort study conducted by the MAH.

Methods

Study participants

Main criteria for inclusion

1. Aged from birth to less than 30 months of age at the time that glycopyrronium bromide was commenced.

2. Treated with glycopyrronium bromide for sialorrhoea (or equivalent terminology) via the enteral route.

Main criteria for exclusion

1. Treatment with glycopyrronium bromide for other reasons than sialorrhoea.

2. Aged 30 months or over at the time that glycopyrronium bromide was commenced.

3. Glycopyrronium bromide given by a route other than the enteral route.

Treatments

Enteral glycopyrronium bromide. Not further detailed in the interim analysis.

Objectives

1. Evaluate the safety of enteral glycopyrronium bromide, administered for the symptomatic treatment of sialorrhoea in paediatric patients below 3 years of age, in terms of adverse events, suspected serious adverse events and the associated treatment discontinuation due to such events.

2. Evaluate the efficacy of enteral glycopyrronium bromide, administered for the symptomatic treatment of sialorrhoea in paediatric patients below 3 years of age, using appropriate scales, review of symptoms, time to other treatments and discontinuation due to treatment failure.

Outcomes/endpoints

The efficacy of glycopyrronium bromide will be measured by:

A change in a drooling severity scale such as the DIS, mTDS or other relevant scale. In the absence of any formal rating scale any other terminology/ description/ indication that there has been no change, an improvement, or worsening of drooling or sialorrhoea symptoms will be reviewed.

Number of participants where glycopyrronium bromide is discontinued due to treatment failure.

Assessors comment

The inclusion and exclusion criteria are considered relevant for evaluating the efficacy for this extension of indication to include children aged 2-3 years. Objectives and endpoints are also acceptable.

The treatment used was enteral glycopyrronium bromide, not further detailed in the interim analysis. The MAH is asked to identify the formulations used and identify the compositions and discuss the impact of the different formulations/excipients on the pharmacokinetics and justify that the composition and release characteristics of the marketed product Sialanar are sufficiently similar to the products used in this study. **(MO)**

Sample size

N/A

Randomisation and blinding (masking)

N/A

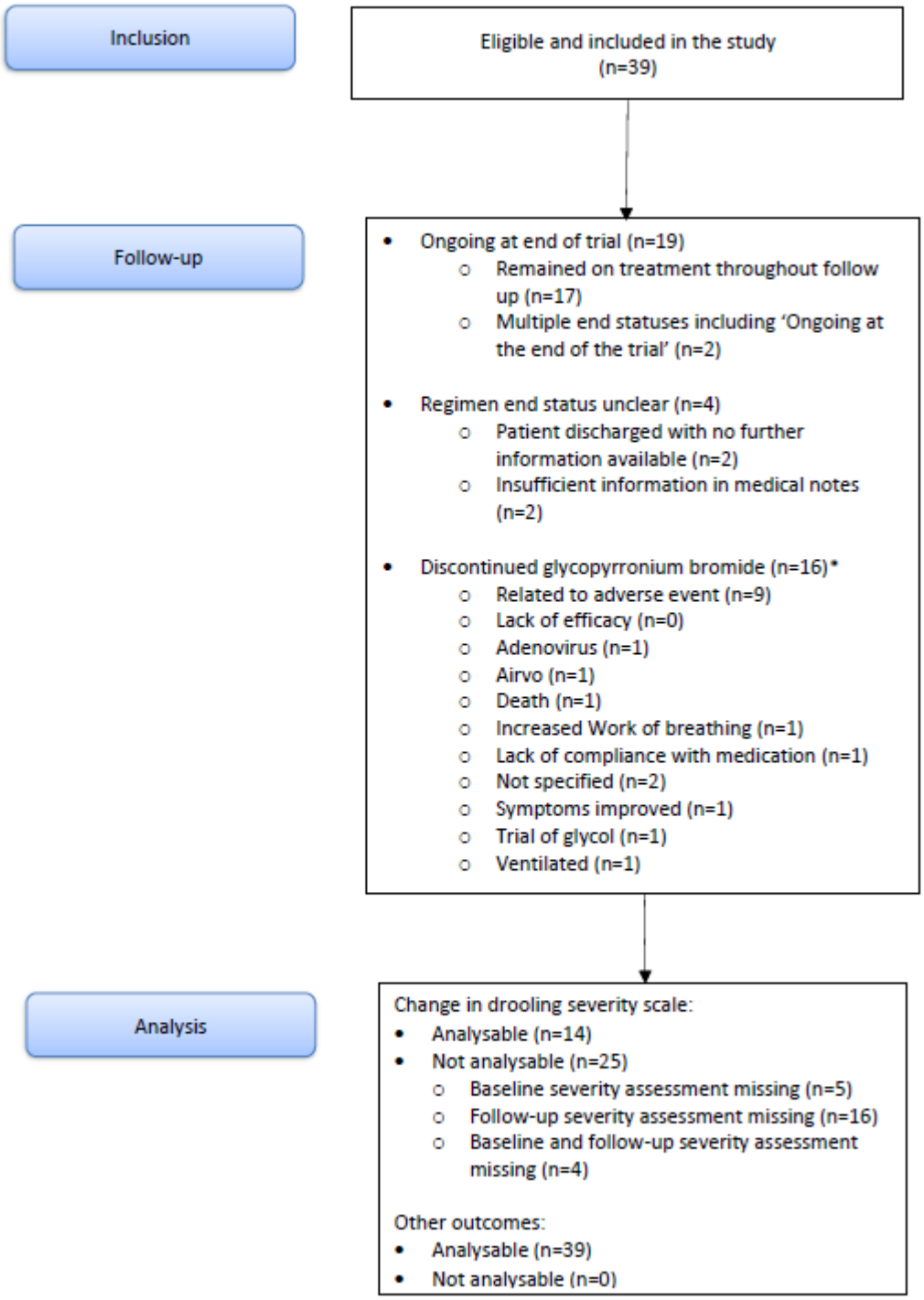
Statistical methods

N/A

Results

Participant flow

Figure 4-1 Flow diagram



Recruitment

Patients were recruited from 3 centers in United Kingdom.

First patient was assessed for eligibility on: 25/08/2023.

Patients with data entered up to: 11/12/2023.

Conduct of the study

There have been no serious breaches of GCP or the trial protocol.

Baseline data

Table 4-2 Demographic details

	Total
Sex: n (%)	(N=39)
Female	13 (33.3%)
Male	26 (66.7%)
Missing	0
Age started glycopyrronium bromide (years)	(N=39)
N*	38
Mean (SD)	0.97 (0.69)
Median (IQR**)	0.81 (0.42, 1.63, 1.20)
Range	[0.02, 2.46]
Missing	1
Gestational age at birth (weeks)	(N=39)
N*	35
Mean (SD)	36.83 (3.40)
Median (IQR**)	38.00 (34.71, 38.43, 3.72)
Range	[26.57, 42.00]
Not known	0
Missing	4
Body weight at birth (kg)	(N=39)
N*	30
Mean (SD)	2.66 (0.81)
Median (IQR**)	2.71 (2.07, 3.29, 1.22)
Range	[0.97, 4.05]
Not known	0
Missing	9
Body length at birth (cm)	(N=39)
N*	0
Mean (SD)	
Median (IQR**)	
Range	
Not known	
Missing	39

* *N in the brackets is a sum of N* and the missing and not known categories as applicable, **IQR=LQ, UQ, IQR.*

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Table 4-3 Medical history

	Total
Underlying diagnosis causing sialorrhoea[1]: n (%)	(N=39)
Cerebral palsy	8 (20.5%)
Epilepsy	9 (23.1%)
Biphasic stridor	1 (2.6%)
Central apnoeas, Obstructive apnoeas	1 (2.6%)
Centronuclear myopathy with hypotonia	1 (2.6%)
Centronuclear myotubular myopathy (SPEG gene mutation)	1 (2.6%)
Complex medical needs - no unifying diagnosis	1 (2.6%)
Congenital diaphgragmatic hernia	1 (2.6%)
Congenital myotonic dystrophy type 1	1 (2.6%)
Dandy walker malformation with large interhemispheric cyst	1 (2.6%)
Epileptic encephalopathy with central hypotonia	1 (2.6%)
Hydrocephalus	1 (2.6%)
Hypoxic Ischemic Encephalopathy	1 (2.6%)
Loss of material from chromosome 16	1 (2.6%)
Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome	1 (2.6%)
Myelomeningocoele	1 (2.6%)
Myotubular myopathy - hemizygous variant in MTM1 gene	1 (2.6%)
Pfeiffer syndrome	1 (2.6%)
Phelan McDermid Syndrome	1 (2.6%)
Spinal muscular atrophy	3 (7.7%)
Trisomy 8 Mosaicism	1 (2.6%)
UBA5 gene mutation	1 (2.6%)
UFM1 gene homozygous 3bp deletioj	1 (2.6%)
Undiagnosed neurodevelopmental disorder	2 (5.1%)
Undiagnosed neuromuscular disorder	1 (2.6%)
VACTERL	1 (2.6%)
WWOX epileptic encephalopathy	1 (2.6%)
X-linked myotubular myopathy	1 (2.6%)
bulbar dysfunction	1 (2.6%)
epilepsia partialis continua phenotype	1 (2.6%)
presumed cow's milk allergy	1 (2.6%)
severe drug resistant epilepsy	1 (2.6%)

Numbers analysed

N= 39

Outcomes and estimation

4.6.1 Drooling severity scale

Table 4-18 Completeness of drooling severity scales at baseline, 6 weeks and final follow-up

		Baseline n (%)	6 weeks[1] n (%)	Final follow-up n (%)
Has a drooling severity scale assessment:		(N=39)	(N=39)	(N=39)
	Yes	30 (76.9%)	19[2] (48.7%)	19[2] (48.7%)
	No	9[3] (23.1%)	20 (51.3%)	20 (51.3%)
Drooling severity scale assessment available:		(N=30)	(N=19)	(N=19)
	Drooling Impact Scale	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Modified Teacher's Drooling Scale	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other	30 (100.0%)	19 (100.0%)	19 (100.0%)

[1] Since the length of follow-up may be different for each patient, 6 weeks has been chosen as a common follow-up timepoint across patients. The closest severity follow-up to 6 weeks is used as the 6-week follow-up.

[2] Five patients with follow-up drooling severity scale assessments do not have a baseline drooling severity scale assessment.

[3] Of the nine patients with no baseline drooling severity scale assessment: three are missing, four had no data and two had unclear data.

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Table 9. Other treatments/interventions for sialorrhoea started whilst patient still on glycopyrronium

	Occurrences n	Number of patients n (%)
n	-	39
Started another treatment for sialorrhoea while still on glycopyrronium bromide: n (%)	-	16 (41.0%)
Reasons for starting another treatment[1,2]:	**30**	16
Airway assessment	3	1 (6.3%)
Anxiety	1	1 (6.3%)
Community respirator	1	1 (6.3%)
Delayed Speech	1	1 (6.3%)
Distress	1	1 (6.3%)
Dystonia	3	2 (12.5%)
End of life care	1	1 (6.3%)
Excess secretions	10	9 (56.3%)
Hyoscine started	1	1 (6.3%)
Increased secretions	3	3 (18.8%)
Secretions	1	1 (6.3%)
Secretions removed by	1	1 (6.3%)
Secretions too thick	1	1 (6.3%)
Thermal epiglottopexy	2	1 (6.3%)
Other treatments for sialorrhoea[2]:	**21**	16
7% Sodium Chloride Nebuliser (2 mls)	1	1 (6.3%)
Botox	1	1 (6.3%)
Hyoscine Hydrobromide (0.25 patch)	1	1 (6.3%)
Midazolam (500 microgram)	1	1 (6.3%)
Other - 0.9% Sodium Chloride Nebuliser	1	1 (6.3%)
Other - 3% sodium chloride nebulisers	1	1 (6.3%)
Other - Adenotonsillectomy	1	1 (6.3%)
Other - Hyoscine Hydrobromide	5	5 (31.3%)
Other - Microlaryngotracheobronchoscopy	2	1 (6.3%)
Other - Suction	1	1 (6.3%)
Other - Tracheostomy	1	1 (6.3%)
Other - Trihexyphenidyl hydrochloride	1	1 (6.3%)
Other - thermal epiglottopexy	1	1 (6.3%)
Speech and language therapy	1	1 (6.3%)
Trihexyphenidyl hydrochloride (2 mg)	1	1 (6.3%)
Trihexyphenidyl hydrochloride (2 milligrams)	1	1 (6.3%)

1 Reasons are not mutually exclusive per drug prescribed.

2 Four treatments started prior to first dose but continued while on glycopyrronium bromide.

Table 4-13 Premature discontinuation of glycopyrronium bromide

	Total n (%)
Discontinued glycopyrronium bromide: n (%)	16 (41.0%)
Reasons for discontinuing[1]:	
Related to adverse event	9 (56.3%)
Lack of efficacy	0 (0.0%)
Adenovirus	1 (6.3%)
Airvo	1 (6.3%)
Death	1 (6.3%)
Increased Work of breathing	1 (6.3%)
Lack of compliance with medication	1 (6.3%)
Not specified	2 (12.5%)
Symptoms improved	1 (6.3%)
Trial of glyco	1 (6.3%)
Ventilated	1 (6.3%)

[1] The 1st discontinuation of glycopyrronium bromide has been considered in this table.

Dosing information

Real-world data provides information on the doses used in 39 children under the age of 3 years. The mean starting dose was 24.9 mcg/kg/dose (range 5.8 to 54.4 mcg/kg/dose), in line with the Sialanar dosing table and falling between Dose level 1 (16 mcg/kg/dose) and Dose level 2 (32 mcg/kg/dose) (Sialanar SmPC expressed as glycopyrronium bromide). As expected, the initial dose range is wide with some children being started on a fraction of the equivalent licensed dose (5.8 mcg/kg/dose) and some starting on 54.4 mcg/kg/dose (i.e. between Dose level 3 (48mcg/kg) and Dose 4 (64 mcg/kg)).

Treatment was mainly given three times daily (22/39), (range 1 to 4 times per day). This is entirely in line with known dosing patterns for glycopyrronium in children 3 years and older, and in line with the data from the SALIVA study. It is likely that those starting on a higher dose level were transferred from another treatment or were already titrated on glycopyrronium at the point of first entry in the hospital notes.

Assessors comment

In this interim analysis, 39 children under 3 years of age treated with enteral glycopyrronium bromide for Sialorrhea were included. The most common cause for sialorrhea in the interim analysis was epilepsy (23.1%), followed by cerebral palsy (20.5%) and Spinal muscular atrophy (7.7%).

There is no available data for DIS to compare with the SALIVA study. However, in table 4-18 it is stated that some "Other" drooling severity scale assessments are available. The MAH is asked to provide an analysis of this data, if this are considered relevant to support the efficacy of glycopyrronium bromide in children aged 2-3 years. **(OC)**

16 children were prescribed an additional intervention at some point whilst remaining on glycopyrronium bromide. The treatments included hyoscine (6/16), trihexyphenidyl (3/16) and Botox (1/16). The MAH states that the additional interventions indicate the severity of the drooling and the continuation of glycopyrronium indicate its continued usefulness. The is acknowledged.

41.1% discontinued glycopyrronium bromide during the studied period. Most discontinuities were due to adverse events (56.3%) or not specified (12.5%). None of the discontinuations were due to lack of efficacy.

The presented real-world data may be used to support the use of glycopyrronium bromide in children aged 2-3 years, however there are uncertainties related to the data, e.g. which GB product has been used **(MO)**, which drooling scale was used to evaluate efficacy etc.

3.4.2.4. Lovardi et al. (2022): Glycopyrrolate for drooling in children with medical complexity under three years of age

A case report of eighteen children under three years of age, followed by a multidisciplinary team at the Bambino Gesù Children Hospital.

Methods

Study participants

All patients were followed by a multi-disciplinary team at the Bambino Gesù Children Hospital. Eighteen children with medical complexity who were younger than 3 years of age, received Glycopyrronium bromide treatment in off label setting.

Treatments

Glycopyrronium bromide.

Objectives

The aim of the study is to determine that Glycopirrolate is safe and effective in decreasing drooling in children with medical complexity under 3 years of age.

Outcomes/endpoints

The response to treatment was assessed according to the Drooling Impact Scale at time 0 and time + 1 month.

Assessors comment

Lovardi et al. 2022 is a single arm prospective case study in children under 3 years of age with medical complexity receiving Glycopyrronium bromide for treatment of drooling.

The objectives and outcomes are acceptable.

The treatment used was glycopyrronium bromide tablets, not further detailed in the study report. The MAH is asked to justify that the composition and release characteristics of the marketed product Sialanar applied for are sufficiently similar to the products used in this study. **(MO)**

Sample size

N/A

Randomisation and blinding (masking)

N/A

Statistical methods

N/A

Results

Participant flow

Not available.

Recruitment

Not available.

Conduct of the study

All the participants and their parents gave informed consent before starting the experimental sessions. The procedure was approved by Ethics Committee of Bambino Gesù Children's Hospital (Rome, Italy).

Baseline data

Table 1 Patients charactheristics

Patients	18
Age	
Median	17.5 months
Range	2–36 months
< 12 months	6 patients
Sex	
Male	10
Female	8
Weight	
Median	9.8 kg
Range	3.5–22 kg
Diagnosis	
CEREBRAL PALSY	9
Genetic/Malformative	9
COGNITIVE IMPAIRMENT	100%
Speech Anomalies	100%
Gastrostomy	
Yes	16
No	2
Tracheostomy	
Yes	12
No	6
Mechanical Ventilation	
Yes	2
No	16

Numbers analysed

N=18

Outcomes and estimation

The mean Drooling Impact Scale at time 0 was 89 (range 81–100) and after 1 month 61 (range 43–78); the difference was statistically significant ($P < 0.001$). Considering patients who presented a decrease in the Drooling Impact Scale after 1 month, the overall response to treatment was 94%; one patient stopped treatment soon after the first month for lack of efficacy while in two patients the treatment was discontinued after 6 months after medical and parental decision to perform the salivary duct ligation. In one patient, treatment was discontinued after 9 months for urinary retention that had no clear relationship with Glycopyrronium bromide administration.

Glycopyrronium bromide was the first medical treatment for drooling in 17 out of 18 patients; one patient received intradermal scopolamine before GLY that was discontinued for toxicity. At median follow-up of 31.5 (range 1–69 months) from starting treatment, 14 patients continue the GLY adjusting the dose according to the weight gain.

Dosage data

Lovardi et al. (2022) shows the use of a median starting dose of 65 mcg/kg/day (range 20–210 mcg/kg/day glycopyrronium bromide) given in three divided doses (i.e. approx. 22mcg/kg/dose), with a median maintenance dose of 70 mcg/kg/day (range 20–280 mcg/kg) (i.e. approx. 23mcg/kg/dose). The wide range in doses was due to the need to use a 0.5mg tablet which resulted in the dose for low weight patients being a relatively high dose/kg. There was little apparent movement in the dose of glycopyrronium in this study, likely a result of the limited ability to titrate the dose due to the use of the 0.5mg tablet and sufficient efficacy/tolerability in the patient population. Nevertheless, as shown by the efficacy and safety data, the dose was effective and well tolerated. The median dose per administration was 22 to 23 mcg/kg. This is in line with the Sialanar dosing table and shows the median starting dose in Lovardi et al. (2022) falling between equivalent of Dose level 1 (16 mcg/kg) and Dose level 2 (32 mcg/kg) (Sialanar SmPC).

Assessors comment

In this case report by Lovardi et al of 18 children under three years of age, all patients received Glycopyrronium bromide for the treatment of drooling. Nine patients had cerebral palsy and nine a genetic/malformative syndrome.

Response to treatment was assessed according to the Drooling Impact Scale administered at time 0 and after 1 month.

The mean Drooling Impact Scale (DIS) at time 0 was 89 (range 81–100) and after 1 month of treatment was 61 (range 43–78); the difference was statistically significant ($P < 0.001$). The change is considered clinically relevant.

Even though the study has limitations due to the study design (e.g. single arm trial, use of different formulation of Glycopyrronium bromide), the results may overall support the efficacy of Glycopyrronium bromide in children aged 2-3 years with chronic neurological disorders.

3.4.2.5. Summary of main studies

Not applicable.

Analysis performed across trials (pooled analyses and meta-analysis)

The MAH provided a broad description of the studies mentioned above as an analysis across the trials. Results of these studies were not statistically analysed (not possible to compare due to methodological differences) and therefore there are no new results presented. Therefore, the assessment is the same as for efficacy results for the individual studies.

Clinical studies in special populations

No clinical studies in special populations were submitted by the MAH which was considered acceptable.

Supportive studies

No further studies were submitted.

3.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

No randomised, double-blind, placebo-controlled trial has been submitted that include the sought population, namely the 2-3 years old children. Feasibility issues associated with conducting a randomized, double-blind controlled study in children younger than 3 years are acknowledged, especially with regard to the severity of the disease and the rate of off-label use of the glycopyrronium products in clinical practice. However, it needs to be considered in the overall evaluation, that the submitted evidence in this population is based on observational, retrospective data and case series. Hence, the quality of the data that the decision on benefit-risk is to be based on are liable to confounding and bias. This needs to be considered in the overall evaluation.

In addition, no dose response studies within the clinical efficacy data package were provided; instead, analysis of clinical information relevant to dosing recommendation was presented.

The data submitted to inform on the pharmacokinetics of glycopyrronium in the paediatric population, is the same as in the initial PUMA. It is a study by Rautakorpi 1994 evaluating a single dose of IV glycopyrronium in 26 children undergoing minor surgery. Data are limited, but the PK of glycopyrronium does not seem to differ from those aged 3 years and above. The low and variable oral absorption defines the need for a slow titration phase based on the patient's weight as recommended in the SmPC. However, the data is not considered sufficient to use as a PK bridge.

Children with cerebral palsy and other neurological disorders often have a lower weight compared to healthy children of the same age. The weight charts for children with cerebral palsy show that the lowest weight for a 2-year-old is around 6kg. Dosing of Sialanar in the SmPC is given as the base (glycopyrronium), rather than the salt (glycopyrronium bromide) nevertheless the evidence below is presented in mcg/ml of glycopyrronium bromide where possible to allow comparison across datasets.

Both the Real-World Data (PRO/GLY/005) and Lovardi et al. (2022) data support the use of glycopyrronium bromide at a starting dose of 22 to 25 mcg/kg per dose given three times daily in children under 3 years of age. This is in line with the existing SmPC for Sialanar and corresponds to Dose levels 1 to 2.

According to the SmPC for Sialanar, the mean daily starting dose for children aged 3 to 17 years is 48 mcg/kg/day, (16mcg/kg/dose glycopyrronium bromide ~ 12.8mcg/kg/dose glycopyrronium) titrated slowly by increments of 48 mcg/kg/day (16mcg/kg/dose ~ 12.8mcg/kg/dose glycopyrronium) at weekly intervals for up to 4 additional dose increases. The median daily starting dose in the Lovardi et al. (2022) study was between the 1st (48 mcg/kg/day or 16mcg/kg/dose) and 2nd (96 mcg/kg/day or 32mcg/kg/dose) dose titrations as per the range given in the SmPC.

Maintenance doses, based on Dose Level 3 of the dose titration schedule in the SmPC are 144 mcg/kg/day (48mcg/kg/dose glycopyrronium bromide ~ 38.4mcg/kg/dose glycopyrronium). Data from the Lovardi et al. (2022) study suggests that clinicians are more cautious with dose titration and remain at the lower end of the range median 23mcg/kg/dose (range 6.7 to 93mcg/kg/dose).

The treatment used in Lovardi et al. (2022) was glycopyrronium bromide 0.5 mg tablet and treatment used in PRO/GLY/005 and Papandreou 2024 was enteral glycopyrronium bromide, not further detailed in the study report. No difference in pharmacokinetics is expected in children aged 2 to 3 years compared to children aged 3 years and older. The similarity in dosage applied in children younger than 2 years comes only from the publication of Lovardi et al. (2022) and RWD PRO/GLY/005, where no information was provided on the glycopyrronium formulation used in the study population. Because

oral absorption has been shown to be variable, information about study medication is essential to assess the bioavailability of various glycopyrronium-containing products. The MAH is asked to justify that the composition and release characteristics of Sialanar are sufficiently similar to the products used in the studies. **(MO)**

The data provided shows that children under the age of 3 years are dosed at or below the licensed dose range of 16mcg/kg per dose to 80mcg/kg/dose glycopyrronium bromide, depending on the weight and where the child is in the dosing schedule. The MAH proposed a conservative lowest dose of 8kg and used the current dosing regimen in the SmPC. The dose of Sialanar (320mcg/ml) for children between 8 and 12 kg would range from 0.4mls to 2.0mls (16 to 96mcg/kg/dose of glycopyrronium bromide) depending on the weight of the child and where they are in the titration schedule. The SmPC has been updated to reflect the dosing schedule in children from 2 to 3 years of age (8 to 12kg). This is considered appropriate provided resolution of the MO above.

New evidence supporting efficacy in the present indication

The SALIVA study is new and was not submitted at the initial MAA. It is a double-blind, placebo-controlled, randomised clinical trial comparing the efficacy and safety of Sialanar against placebo in children and adolescents with severe sialorrhoea and neurodisabilities. The primary objective was to measure the efficacy of Sialanar compared with placebo for the treatment of children with severe sialorrhoea related to chronic neurodisabilities. The doses and titration used in the study was the same as recommended in the Sialanar SmPC. Overall, the study objectives and treatments are acceptable. But the SALIVA study **did not** include the age group (children aged 2-3 years) applied for in this extension of indication variation. The MAH states that the study can be used to compare efficacy data for children aged 2-3 years. In the SALIVA study the primary endpoint was the change in the validated French edition of the Drooling Impact Scale (DIS-F) score from baseline to day 84. The possible score ranges from 10 to 100, with the higher scores indicating greater severity and impact. The minimally clinically important difference was 13.6 points. Overall, the DIS-F endpoint is considered acceptable as it is a validated tool and the clinically important difference of 13.6 points is considered adequate as similar clinically important differences is used in the literature e.g. Reid 2019 and Papandreou et al. 2024.

The MAH is requested to provide number of children at the different ages (3 years old, 4 years old etc.) to see how many children in the lower ages were included in the trial **(OC)**

Evidence supporting efficacy in the 2-3 years old children

There are no RCTs to support the efficacy in 2-3 year old children. Only RWD like observational cohort studies and case series have been submitted that include data on children below 3 years of age. However, the data that the decision on benefit-risk is to be based on are liable to confounding and bias. This needs to be considered in the overall evaluation.

As a primary efficacy outcome, the supportive Cohort study (Papandreou et al. 2024) and case series (Lovardi et al. 2022), including children below 3 years of age, used the Drooling Impact Scale (DIS) score and not the DIS-F score as in the SALIVA study. The MAH is asked to discuss the differences between the DIS and DIS-F score and justify that the endpoints can be compared between the studies, to be able to indirect compare the effect in the different age groups, with the known methodological constraints of such comparison. **(OC)**

For the observational studies being compared to the result of the SALIVA study, means are presented. MAH is requested to clarify the potential impact of comparing median to means from the studies, when comparing results. **(OC)**

Papandreou 2024

The study was a single center cohort study. The objective was to compare efficacy and side effect profile data on conservative, behavioural, pharmacological, and surgical treatments used for pediatric saliva control. The study included patients under 18 years, including patients in the age-group 2-3 years as applied for in this extension of indication variation. Patients were offered different treatment, including weight-based Glycopyrronium Bromide in a different dose-range than in the SALIVA study.

One of the endpoints were DIS before interventions and every 3 months afterwards, with a minimum follow-up time of 12 months. A minimal clinically important of difference in the score of >10 was reported as reliable, a score of 20-28 a good outcome, and a score of >28-38 being very good to excellent.

There are several limitations to the study design; Specific inclusion and exclusion criteria are not mentioned, the dose-ranges differ from the dose-ranges in the Sialanar SmPC and SALIVA study and patients were not randomized and blinded.

PRO/GLY/005

PRO/GLY/005 is a retrospective analysis of real-world evidence on the use of glycopyrronium bromide in children under 3 years of age with sialorrhea. Main criteria for inclusion were aged from birth to less than 30 months of age at the time that glycopyrronium bromide was commenced and treated with glycopyrronium bromide for sialorrhoea via the enteral route. Treatments were enteral glycopyrronium bromide, not further detailed in the interim analysis. Primary objectives were safety and efficacy enteral glycopyrronium bromide, administered for the symptomatic treatment of sialorrhoea in paediatric patients below 3 years of age, was secondary objective.

The inclusion and exclusion criteria are considered relevant for evaluating the efficacy for this extension of indication to include children aged 2-3 years. Objectives and endpoints are also considered acceptable.

Lovardi et al. 2022

Lovardi et al. 2022 is a single arm prospective case study in children under 3 years of age with medical complexity receiving Glycopyrronium bromide for treatment of drooling.

The objectives and outcomes are acceptable. However, there are several limitations to the design; Specific inclusion and exclusion criteria are not mentioned, and patients were not randomized and blinded.

Endpoints used in the initial MAA

In the initial PUMA the main studies (Zeller 2012a and Mier et al 2010) used the modified 9-point Teacher's Drooling Scale (mTDS) as primary endpoint and therefore it is difficult to compare the new published studies with the studies from the initial PUMA.

The SALIVA study and Real World Data interim analysis was performed in accordance with GCP as claimed by the MAH. The other studies are submitted as published literature. There is no statement about GCP compliance for the published studies.

Overall, the design of the studies to support the efficacy of glycopyrronium bromide in children aged 2-3 years are hampered by the nature of real-world data and literature data, with single arm trial design, not blinded or randomized and with sparse information on eligibility criteria. Further, the different study designs, different statistical methods, endpoints and different formulations and doses, makes it difficult to compare the results between the studies. However, since the pharmacokinetics of glycopyrronium bromide in children aged 2-3 years does not seem to differ from those aged 3 years and above and severe sialorrhoea (chronic pathological drooling) in children aged 2-3 years compared

to 3 years and above are expected to have the same pathophysiology, support of efficacy from these data may be considered acceptable if the MAH can provide data on the sought population.

Efficacy data and additional analyses

SALIVA study

In total, 88 children were enrolled, and of these, 87 were randomized and included in the full analysis set and modified intention-to-treat populations (mITT).

The most common cause for sialorrhea in the Sialanar group was cerebral palsy (43.2%), followed epilepsy (31.8%) and intellectual disability (27.3%).

A significant median change at D84 from baseline was seen for the primary endpoint DIS-F with Sialanar compared to Placebo [Q1, Q3]; (−29.5 [−44.5, 0] vs −1 [−16, 5]; $p < 0.001$). The change for the Sialanar treatment arm is considered clinically relevant with a minimal clinical important difference of 13.6 points. The same clinically relevant change was seen for the secondary endpoint at D28 (−25 [−43, −0.5] vs −2 [−21, 1]; $p < 0.01$).

Although the SALIVA trial is a double-blind, placebo-controlled, randomized clinical trial comparing the efficacy and safety of Sialanar versus placebo in children and adolescents with severe sialorrhea and neurodisability, it cannot be considered the main study supporting the proposed variation since it did not include any children under 3 years of age. The study can be used to compare efficacy with the following studies including children 2-3 years of age due to similar efficacy endpoints (DIS/DIS-F). However, this direct comparison has several limitations (different drooling scale used, no information about inclusion and exclusion criteria, randomization, study medication etc.). In the initial PUMA the main studies (Zeller 2012a and Mier et al 2010) used the modified 9-point Teacher's Drooling Scale (mTDS) as primary endpoint and therefore it is difficult to compare the new published studies with the studies from the initial PUMA.

Papandreou 2024

In total, 483 children and adolescents (age range, 20 months to 19 years) were included in the study.

The most common cause for sialorrhea in the cohort was cerebral palsy (48.4%), followed by genetic or syndromic conditions (17.8%) and progressive neurometabolic conditions (8.1%).

150 of the included children and adolescents were treated with glycopyronium bromide. From the data given in the article it cannot be concluded how many children that was included in the age-group 2-3 years and further it cannot be concluded, if any of the children aged 2-3 years were treated with glycopyronium bromide. This is a crucial limitation for this study with regard to supporting the efficacy in children aged 2-3 years. The MAH is asked to justify that this study can be used to support the efficacy and use of glycopyronium bromide in children aged 2-3 years. **(MO)**

With regard to the efficacy of glycopyrronium bromide in the study, a mean change in DIS (95% CI) of 21.54 (19.7-24.81) was reported. This is similar the reported median change of −29.5 on the DIS-F in the SALIVA study. However, from the data provided in this cohort study it is difficult to compare the efficacy of glycopyrronium bromide in children aged 2-3 years with to the SALIVA study due to the missing details on age range in the glycopyrronium bromide group.

PRO/GLY/005

In this interim analysis, 39 children under 3 years of age treated with enteral glycopyrronium bromide for Sialorrhea were included. The most common cause for sialorrhea in the interim analysis was epilepsy (23.1%), followed by cerebral palsy (20.5%) and Spinal muscular atrophy (7.7%).

A population of patients relevant to the proposed variation was included in the study, so it could be possible to obtain the necessary information regarding the efficacy and safety of glycopyrronium bromide from this retrospective analysis of real-world evidence. There is no available data for DIS to compare with the SALIVA study. However, in table 4-18 it is stated that some "Other" drooling severity scale assessments are available. The MAH is asked to provide an analysis of this data, if this are considered relevant to support the efficacy of glycopyrronium bromide in children aged 2-3 years. **(OC)**

16 children were prescribed an additional intervention at some point whilst remaining on glycopyrronium bromide. The treatments included hyoscine (6/16), trihexyphenidyl (3/16) and Botox (1/16). The MAH states that the additional interventions indicate the severity of the drooling and the continuation of glycopyrronium indicate its continued usefulness. This is noted.

41.1% discontinued glycopyrronium bromide during the studied period. Most discontinuities were due to adverse events (56.3%) or not specified (12.5%). None of the discontinuations were due to lack of efficacy.

These real-world data may be used to support the use of glycopyrronium bromide in children aged 2-3 years if it is possible to evaluate the efficacy.

Lovardi et al. 2022

In this case report of 18 children under three years of age, all patients received Glycopyrronium bromide for the treatment of drooling. Nine patients had cerebral palsy and nine a genetic/malformative syndrome.

The mean DIS at time 0 was 89 (range 81–100) and after 1 month of treatment was 61 (range 43–78); the difference was statistically significant ($P < 0.001$). The change is considered clinically relevant and was similar to the median change reported in the SALIVA study.

The SALIVA study didn't include children in the applied age-group, but serves as a comparator for the other studies for the primary endpoint. Due to uncertainties regarding children included in the age-group 2-3 years, the data from the Papandreou 2024 study is not considered to supporting the efficacy in children aged 2-3 years, unless the MAH can provide data in the sought age-group. **(MO)** The PRO/GLY/005 study did not provide and efficacy endpoint data, but the data include the use of Glycopyrronium bromide in the applied age-group. The Lovardi 2022 study include the use of Glycopyrronium bromide in the applied age-group and even though the study has limitations due to the study design, the result may support the efficacy of Glycopyrronium bromide in children aged 2-3 years with chronic neurological disorders. The MAH is asked to update the SmPC section 5.1 with relevant data on efficacy for children aged 2-3 years (if approved) and the data from the SALIVA study in children aged 3-17 years (according to the paediatric regulation). **(OC)**

As discussed above, the efficacy data in children aged 2-3 years is limited, and it is questioned if the data presented is considered acceptable even though it seems that the pharmacokinetics of glycopyrronium bromide in children aged 2-3 years does not differ from those aged 3 years and above (based on an IV, single-dose trial). However, this is not considered sufficient as a PK bridge. Severe sialorrhoea (chronic pathological drooling) in children aged 2-3 years compared to 3 years and above are expected to have the same pathophysiology.

PDCO

The PIP granted for the PUMA is from 2 to less than 18 years of age. PDCO determined that the waiver should be granted according to the clinical need, from 2 years of age.

Overall summary of efficacy

At the time of the initial PUMA there was insufficient information on the efficacy and safety of glycopyrronium to support use below 3 years of age.

To support the extension of indication to include children 2-3 years of age, the evidence is based on observational, retrospective data and case series. Results from a randomised, double-blind, placebo-controlled trial has been submitted, but this trial does not include children below the age of 3 years. Hence, the quality of the data that the decision on benefit-risk is to be based on are liable to confounding and bias. Although the submitted evidence include children below the age of 3 years, the Applicant has not provided data nor discussed the efficacy specifically for this patient population. Although it could be anticipated that efficacy will be the same, it is of major importance that the Applicant address the efficacy in the sought population. **(MO)**

Additional expert consultation

N/A

Assessment of paediatric data on clinical efficacy

All date submitted were paediatric data.

3.4.4. Conclusions on the clinical efficacy

The efficacy data in children aged 2-3 years is limited and the design of the studies to support the efficacy of glycopyrronium bromide in children aged 2-3 years are liable to confounding and bias due to the nature of real-world data and literature data. It is therefore questioned if the data presented is considered acceptable.

3.5. Clinical safety

3.5.1. Introduction

The original marketing authorization was based primarily on three pivotal, published Phase III clinical trials in patients aged 3 years and above (Zeller 2012a, Zeller 2012b and Mier 2000). In these studies, most of the adverse events that occurred more frequently in patients treated with glycopyrronium, than in patients on placebo, were typical anticholinergic effects. They included dry mouth/excessive dryness of mouth or secretions, constipation, vomiting, nasal congestion, flushing, behavioural changes, urinary retention and diarrhoea. Overall, these AEs were frequent in patients treated with glycopyrronium (frequencies ranging from 10 to 40%). Mier (2000) reported that 23% of the children treated with glycopyrronium had behavioural changes. Urinary retention was not observed in the placebo group in either of the placebo-controlled studies but occurred in 13-15% of the patients treated with glycopyrronium. Pneumonia was also a frequent adverse event in the Zeller 2012b study and increased with increasing dose, which suggests a causal relationship. In Zeller et al 2012b, fourteen patients (10%) had 20 serious adverse events, 8 while taking the study drug and 6 within 30 days of the last dose. Of these 20 serious adverse events, four were considered treatment-related (nystagmus, oesophageal candidiasis, dehydration and gastrointestinal motility disorder).

In Zeller 2012a 1/19 patients discontinued due to AE in the treatment arm whereas 1/18 discontinued in the placebo arm due to AE. In the open label extension (Zeller 2012b) 10% discontinued due to a treatment related AE. The type of AE, age of the child and doses are unknown. Mier reported 18% (n =

7) withdrawal rate due to an AE. Four discontinued while they were still receiving the lowest dosage level, a mean of 0.04 mg/kg/dose. The other three children discontinued at 10, 28, and 42 days, respectively while receiving a mean dose of 0.06 mg/kg/dose.

It was found by the CHMP that the AE profile established in other populations, as presented by the MAH (e.g. adults with Parkinson's disease), could not readily be extrapolated to a population of children with neurological disorders and considerable comorbidities. The PUMA for Sialanar was granted by the CHMP for 3 years and above, based on the data from the mentioned pivotal studies. According to the PIP there is an unmet need in children aged 2-3 years, but it was found by the CHMP that evidence was lacking on safety and efficacy for children in this age group.

For this Type II variation the Applicant presents new data in support of safety in patients with chronic neurological diseases aged 2-3 years old. For this purpose, the Applicant relies on real-world data generated by the Applicant (PRO/GLY/005), a published case series (Lovardi, 2022) and a published cohort study (Papandreou, 2024). Post marketing, a phase 4, double-blind, placebo-controlled, randomized, parallel, multicenter study was conducted to evaluate efficacy and safety of Sialanar (SALIVA). This study did not include children under 3 years of age but serves as a comparator for the new data presented in children < 3 years of age.

3.5.2. Patient exposure

3.5.2.1. SALIVA: Double-blind, placebo-controlled, randomised clinical trial comparing the efficacy and safety of Sialanar® plus oral rehabilitation against placebo plus oral rehabilitation for children and adolescents with severe sialorrhea *and neurodisabilities.*

The safety population was defined as all patients who received at least 1 dose of any study drug (including controls) during the double-blind phase. Patients were analysed according to the treatment actually received (Sialanar® or placebo). 87 patients were randomly assigned to received Sialanar® (n = 44) or placebo (n = 43) for 3 months. Subsequently, 74 patients entered the 6 month open label extension phase and 65 patients completed the phase at D252 (n = 35 from the ex-Sialanar group and n = 32 from the ex-placebo-group). The median age was 9.9 years (IQR 7.6; 14.7) in the Sialanar® group and 10.2 years (IQR 7.3;14.6) in the placebo group. Vital signs were recorded at baseline, and at D84 weight and height was also recorded, without any further issues identified. Key patient demographics are given below.

Study treatment and exposure is detailed for the blind phase and the OLSE phase in the following two tables. In total patients from the ex-Sialanar group were exposed to Sialanar for a median of 251 days (IQR 245;252) and patients from the ex-placebo group were exposed for a median of 167 days (IQR 161;170).

Patient exposure to Sialanar® and dose modifications other than titration in SALIVA for the blinded phase

Table 5. SALIVA Demographics

		320 µg/mL glycopyrronium *n* = 44	Placebo *n* = 43
	Female sex, *n* (%)	17 (38.6)	25 (58.1)
	Median (Q1, Q3) age, years:months	9:11 (7:7, 14:8)	10:2 (7:4, 14:7)
	Median (Q1, Q3) weight, kg	27.6 (18.4, 36.0)	25.0 (20.0, 40.5)
Neurodisability, *n* (%)	Cerebral palsy	19 (43.2)	24 (55.8)
	Epilepsy	14 (31.8)	14 (32.6)
	Intellectual disability	12 (27.3)	14 (32.6)

Table 19: Study treatment use during the blinded phase, dose modification, temporary interruption and discontinuation (FAS, N=87)

		Sialanar® (N=44)	Placebo (N=43)	FAS Total (N=87)
Exposure time (days) during the blinded phase	Analysed number	44	43	87
	Mean (± SD)	73.6 (± 22.9)	80.4 (± 12.7)	77 (± 18.7)
	Median	83.5	84	84
	Q1-Q3	79-84	84-84	83-84
	Min-Max	3-84	27-84	3-84
Dose modification other than titration	Yes	4 (9.1%)	7 (16.3%)	11 (12.6%)
If yes, reason(s)	Adverse event	4 (100%)	3 (42.9%)	7 (63.6%)
	Insufficient efficacy	2 (50%)	4 (57.1%)	6 (54.5%)
	Other reason	1 (25%)	1 (14.3%)	2 (18.2%)

Patient exposure to and doses of Sialanar® in the OLSE phase:

Table 21: Prescribed dosage and last taken dosage of Sialanar® (OLSE, N=74)

		Ex-Sialanar® (N=37)	Ex-Placebo (N=37)	OLSE population (N=74)
Prescribed initial dose of Sialanar® (mL)	Analysed number	37	37	74
	Mean (± SD)	1.2 (± 0.5)	1.2 (± 0.5)	1.2 (± 0.5)
	Median	1.2	1	1
	Q1-Q3	0.8-1.6	0.8-1.6	0.8-1.6
	Min-Max	0.6-2	0.6-2	0.6-2
Last taken dosage of Sialanar® treatment during the study (mL)	Analysed number	37	37	74
	Mean (± SD)	4.6 (± 1.3)	4.1 (± 1.5)	4.3 (± 1.4)
	Median	4	4	4
	Q1-Q3	3.6-6	3-6	3-6
	Min-Max	1.2-6.3	1.2-6	1.2-6.3
Dose (mL) of study treatment at D168 (± 4 days)	Analysed number	34	32	66
	Mean (± SD)	4.7 (± 1.3)	4.2 (± 1.6)	4.4 (± 1.4)
	Median	4.5	4	4
	Q1-Q3	3.6-6	3-6	3.2-6
	Min-Max	2.8-6.3	1-6	1-6.3
Dose (mL) of study treatment at D252 (± 7 days)	Analysed number	33	31	64
	Mean (± SD)	4.7 (± 1.2)	4.3 (± 1.5)	4.5 (± 1.4)
	Median	5	4	4
	Q1-Q3	3.6-6	3-6	3.5-6
	Min-Max	3-6.3	1.2-6	- 6.3

***3.5.2.2. Papandreou**: A comparative cohort study of children with saliva control issues (n = 483) referred to a specialty Saliva Control service.*

The age group was under 18 years of age. 150 patients received glycopyrronium bromide. The most common cause for sialorrhea was cerebral palsy (48.4%), followed by genetic or syndromic conditions (17.8%) and progressive neurometabolic conditions (8.1%).

Table I. Study cohort characteristics

Primary diagnoses	No. of participants (%)/483	Sex, male:female (232:193)	Age, years, mean (range)
Cerebral palsy*	234 (48.4)	127:107	7.4 (1.8-16.3)
Worster-Drought syndrome	29 (6.0)	21 : 8	9.6 (6.2-14.7)
Autistic spectrum disorder	33 (6.8)	24:9	8.8 (5.1-15.9)
Progressive neurometabolic conditions (eg, Tay Sachs, n = 3; Battens, n = 5; mitochondrial, n = 3)	39 (8.1)	18:21	4.6 (1.9-18.8)
Other genetic/syndromic conditions (eg, Rett, n = 9; Lesch-Nyhan, n = 6)	86 (17.8)	39:47	10.1 (5.5-19.2)
Epileptic encephalopathy	19 (3.9)	10:9	9.2 (4.0-17.5)
Other post brain injury (inflammatory/infective/trauma/tumor)	14 (2.9)	7:7	6.1 (2.5-12.4)
Speech delay/isolated sialorrhoea	29 (6.0)	16:13	8.9 (4.4-15.2)

Clinical follow-up continued every 3 months after the conclusion of the study period. The range of postintervention follow-up was 12.5 to 102.0 months; during this period, ≥ 1 treatment was administered as clinically indicated according to a treatment flowchart. 42 had previously been given oral anticholinergic medication (34/42 glycopyrronium bromide and 8/42 trihexyphenidyl). Of these 42 patients, 11 (26.2%) had ceased treatment owing to constipation (6/42), insomnia (3/42), or

behavioral change (2/42). In line with published algorithms these participants were considered for other interventions, and they did not receive anticholinergic drugs during the study.

Assessors comments

The applicant provides data from the SALIVA study, a double-blind, placebo controlled, randomized clinical trial. This serves as a comparator illustrating safety in the approved indication (children aged 3-18 years with chronic neurological disease). 44 patients were exposed in the blind phase, in the open label extension phase 74 patients were exposed. SALIVA is acceptable as a comparator study as it uses a relevant study design and includes a relevant population (children aged 3 years and above with chronic neurological disease). The number of exposed patients is low. While it is recognized that pathological drooling in children is rare, and thus a lower number of participants can be acceptable, the applicant does not discuss safety data from the original, pivotal studies (Zeller 2012a, Zeller 2012b and Miers, 2000) or post-marketing safety data from the applicants' own database or EUDRAvigilance databases. Pooled safety data is not provided, and the discussion in the clinical overview is formatted as a summary of individual studies. The applicant should clearly present and discuss pooled safety data, in a format that allows assessment of the differences in safety profile, between the approved population (children with chronic neurological disease ≥3 years old) versus the proposed indication (children with chronic neurological disease aged <3 years old). Presentation of pooled safety data in a tabulated format is requested. The data should be appropriately stratified, when possible, e.g. depending on age, population and methodological differences **(OC).**

In support of the extension of indication to include children aged 2-3 years the applicant discusses three new studies (PRO-GLY-005, Lovardi (2022) and Papandreou (2024)). All three include children with chronic neurological disease and sialorrhea, median follow-up was >12 months.

In PRO-GLY-005, a real-world retrospective study, 39 patients aged 0-3 years old are exposed. Four are 2-3 years old at treatment initiation, but a significant number of the patients reach age 2 years during the treatment period (as discerned from 4.8 Appendix, Table 4.25 in the study report). The daily dose used in the study differs significantly (range 6.7 – 163.3 mcg/kg), as well as the duration of treatment (range 0,03 – 25,43 months). 9 children are receiving other treatments for sialorrhea and 16 patients started supplementary treatment for sialorrhea while still on glycopyrronium bromide. This makes it more difficult to evaluate the safety of glycopyrronium bromide in the target population.

In Lovardi (2022), 18 patients aged 2-36 months were exposed. The initial dose was in the range 0,02 – 0,21 mg/kg per day. The duration of the follow-up ranged from 1 to 69 months. The actual number of children aged 2-3 years old, who received glycopyrronium, is not clear.

Papandreou (2024), is a prospective cohort study in which 150 patients (approximately 1/3 of the cohort) are exposed to glycopyrronium bromide. Age is stratified by diagnosis, not by treatment option. In three diagnostic groups children aged < 3 years old were included, with age ranges 1.8-16.3 years (cerebral palsy), 1.9-18.8 years (progressive neurometabolic conditions) and 2.5-12.4 years (other post brain injury). It is not clear how many patients aged 2-3 years old were included. There is no information about the specific age in the patients treated with glycopyrronium bromide. From this point of view, Papandreou (2024), with the currently provided information, cannot be accepted as supportive evidence for safety in the paediatric subgroup in question (2 -3 years of age) **(OC)**.PRO-GLY-005 and Lovardi (2022) include a substantial number of children aged 0-23 months, and especially in children aged 0-12 months old, the safety profile is likely different due to immaturity. If a significant number of children aged 0-12 months are included this may skew the safety profile, potentially towards a different or more severe safety profile, than what is actually the case in patients aged 2-3 years old.

In pediatric indications extrapolation can be acceptable, but in this case, the intended population is medically complex. Children with complex neurological disabilities and several comorbidities, are more

vulnerable to the adverse effects of long-term anticholinergic treatment (e.g. thickening of secretions, urinary retention, constipation, CNS effects). Previously, the CHMP did not find it appropriate to extrapolate from data collected in older children or adults with sialorrhea. **In the current application, extrapolation is not discussed or justified by the applicant**, and the proposed indication is only supported by the presented data. The applicant should provide a table of the exposure in the proposed age group (2-3 years old) including other relevant clinical information (e.g. treatment duration, dose, demographics, relevant medical history). The applicant should justify why the number of included children in the given age group is appropriate, or alternatively, justify why extrapolation may instead be appropriate. As part of this it is requested that the applicant specify the number of children receiving long-term treatment **(MO).**

3.5.2.3. PRO-GLY-005 Real world evidence*: Retrospective observational cohort study (real-world evidence) on the use of glycopyrronium bromide in children aged from birth to 30 months with sialorrhea.*

Glycopyrronium bromide was administered enterally. The observation period was up to 36 months after commencement of glycopyrronium or to the child was 3 years old (whichever occurred first). The study included 39 patients, of these n=4 patients were aged 2-3 years at study initiation whereas the remaining participants were < 2 years old at study initiation.

The most common underlying diagnoses causing sialorrhea was cerebral palsy (20.5%), epilepsy (23.1%), spinal muscular atrophy (7.7%) and undiagnosed neurodevelopmental disorder (7.7%). 17 children remained on treatment throughout follow up (median of 23.3 months, range 6.39-35.9 months, IQR: 14.6 months). In total 20/39 children received treatment with glycopyrronium bromide for more than 12 months. Key demographic details are presented below:

Demography of patients included in PRO-GLY-005

	Total
Sex: n (%)	(N=39)
Female	13 (33.3%)
Male	26 (66.7%)
Missing	0
Age started glycopyrronium bromide (years)	(N=39)
N*	38
Mean (SD)	0.97 (0.69)
Median (IQR**)	0.81 (0.42, 1.63, 1.20)
Range	[0.02, 2.46]
Missing	1

3.5.2.4. Lovardi et al. (2022)*: Prospective case study of children with chronic neurological disease < 3 years of age.*

The study included n = 18 children < 3 years of age (median age 17 months, range 2–36 months). Nine patients had cerebral palsy (Gross Motor Function Classification System class V) and nine a genetic/malformative syndrome. Twelve patients had a tracheostomy and two needed mechanical ventilation. Gastrostomy was present in 16 out of 18 patients. All patients received Glycopyrronium. Median follow-up was 31.5 months (range 1–69 months) from starting treatment.

3.5.3. Adverse events

SALIVA

Adverse events (AEs) were recorded at every visit (clinic visits were at D28, D84, D168, D252 and telephone consults weekly in titration phase and at D56 and D140) from parents or carers, and participants where possible. All SAEs and suspected unexpected serious adverse events (SUSARs) were recorded and reported as per standard EMA guidelines. The carer was asked to stop treatment and seek advice from the investigator in the event of constipation, urinary retention, pneumonia, allergic reaction, pyrexia, very hot weather or changes in behaviour. After evaluating the event, the investigator decided if treatment remained stopped or if it could be continued at a lower dose. The dose changes or interruption was recorded in the electronic record (eCRF) with the reason for the change. AEs considered in the safety analysis were all events, regardless of causality with study drug or seriousness, that occurred from the first intake of study treatment until 3 days after the last intake of study treatment.

In total, 61.4% of children reported any adverse event with 320 mcg/mL glycopyrronium while 65.1% of children reported adverse events with placebo during the 28-day titration period, with respective proportions of 77.3% and 69.8% at day 84 (Table 10). Common AEs occurring more frequently in the glycopyrronium group compared to placebo were vomiting (9.1% vs. 4.7%), dry mouth (6.8% vs. 4.7%), irritability (6.8% vs. 4.7%), epilepsy (6.8% vs. 2.3%), abdominal pain (4.5% vs. 2.3%), nasal congestion (4.5% vs. 2.3%), pyrexia (4.5% vs. 0%), agitation (4.5% vs. 0%), urinary retention (4.5% vs. 0%).

Adverse events depending on study phase

Table 10. Overview of adverse events by period

	Day 0 to day 28		Day 29 to day 84		Day 0 to day 84	
	320 µg/mL glycopyrronium	Placebo	320 µg/mL glycopyrronium	Placebo	320 µg/mL glycopyrronium	Placebo
Number (%) experiencing at least one event	**n = 44**	***n* = 43**	**n = 44**	***n* = 43**	**n = 44**	***n* = 43**
Adverse event	27 (61.4)	28 (65.1)	23 (52.3)	11 (25.6)	34 (77.3)	30 (69.8)
Serious adverse event	5 (11.4)	0 (0)	1 (2.3)	1 (2.3)	6 (13.6)	1 (2.3)
Treatment-related adverse event	17 (38.6)	14 (32.6)	12 (27.3)	2 (4.7)	22 (50.0)	15 (34.9)
Treatment-related adverse event leading to treatment discontinuation	4 (9.1)	1 (2.3)	3 (6.8)	1 (2.3)	7 (15.9)	2 (4.7)
Serious treatment-related adverse event	1 (2.3)	0 (0)	0 (0))	0 (0)	1 (2.3)	0 (0

Treatment-related adverse events (TRAE) were reported by 50.0% of children with glycopyrronium and 34.9% with placebo by day 84. The most frequent treatment-related adverse events were constipation (20.5%), dry mouth (6.8%), and vomiting (6.8%) in the glycopyrronium group and constipation (16.3%), diarrhea (7.0%), and fatigue (7.0%) in the placebo group (Table 11). Other frequent TRAE were epilepsy (glycopyrronium bromide 2 patients (4.5%) versus placebo 0 patients) and psychomotor hyperactivity (glycopyrronium bromide 2 patients (4.5%) versus placebo 0 patients).

Frequent AEs (active treatment versus placebo)

Table 11. Study treatment-related adverse events from day 0 to day 84.

Number (%) experiencing at least one event	320 µg/mL glycopyrronium *n* = 44	Placebo *n* = 43
Constipation	9 (20.5)	7 (16.3)
Dry mouth	3 (6.8)	2 (4.7)
Diarrhoea	1 (2.3)	3 (7.0)
Irritability	2 (4.5)	2 (4.7)
Vomiting	3 (6.8)	0
Flushing	1 (2.3)	1 (2.3)
Urinary retention	1 (2.3)	0

Table 12 summarises the occurrence of AEs in all children treated with glycopyrronium bromide during the OLSE phase, from D84 to D252. In those patients who had been initially treated with glycopyrronium bromide 19 (51.4%) patients had at least one AE during the OLSE phase. Five (13.5%) patients experienced at least one TRAE. In those patients initially treated with placebo, 32 (86.5%) patients had at least one AE during the OLSE phase, and 21 (56.8%) patients experienced at least one TRAE. In the ex-glycopyrronium bromide arm the single TRAE that occurred at least twice was constipation (4 patients (10.8%). In the ex-placebo-arm the TRAEs that occurred at least twice were constipation (12 patients, 32.4%), dry mouth (4 patients, 10.8%) and urinary retention (3 patients, 8.1%).

AEs reported in the open label extension phase

Table 12. Occurrence of AE from D84 to D252 (OLSE, N=74)

> D84 to end of study		Ex-Sialanar® (N=37)	Ex-Placebo (N=37)	OLSE population (N=74)
At least one AE	Yes	19 (51.4%)	32 (86.5%)	51 (68.9%)
	No	18 (48.6%)	5 (13.5%)	23 (31.1%)
At least one AE leading to treatment discontinuation	Yes	2 (5.4%)	4 (10.8%)	6 (8.1%)
	No	35 (94.6%)	33 (89.2%)	68 (91.9%)
At least one expected AE	Yes	10 (27%)	26 (70.3%)	36 (48.6%)
	No	27 (73%)	11 (29.7%)	38 (51.4%)
At least one SAE	Yes	2 (5.4%)	3 (8.1%)	5 (6.8%)
	No	35 (94.6%)	34 (91.9%)	69 (93.2%)
At least one treatment-related AE	Yes	5 (13.5%)	21 (56.8%)	26 (35.1%)
	No	32 (86.5%)	16 (43.2%)	48 (64.9%)
At least one TRAE leading to treatment discontinuation	Yes	2 (5.4%)	4 (10.8%)	6 (8.1%)
	No	35 (94.6%)	33 (89.2%)	68 (91.9%)
At least one expected TRAE	Yes	5 (13.5%)	17 (45.9%)	22 (29.7%)
	No	32 (86.5%)	20 (54.1%)	52 (70.3%)
At least one treatment-related SAE	No	37 (100%)	37 (100%)	74 (100%)

Real world evidence (PRO-GLY-005)

The real-world data generated by the Applicant recorded adverse events (AEs) that were possibly, probably, or definitely related to glycopyrronium bromide. Where a causality assessment had already been made within the medical record this was recorded if a causal relationship was suspected. Where no causality assessment had been made, the investigator completing the data collection made a causality assessment using the validated Liverpool Causality Assessment Tool. If the causality assessment was 'unlikely' the AE was not recorded. If the AE was possibly, probably, or definitely related to glycopyrronium bromide the AE was graded for severity and assessed as to whether the AE would meet the definition of a Serious Adverse Event (SAE). Additional assessments included the dates of occurrence and resolution for all reported AEs and any dose adjustment or cessation of treatment with glycopyrronium bromide in relation to the AE. Following dose adjustment, cessation or re-introduction of treatment, an assessment of resolution, improvement or worsening of that AE was made. Any concomitant medication (including start/stop date and dose) or other treatment/intervention to treat or manage the adverse event was also recorded.

24 non-serious AEs were recorded in 19 patients on glycopyrronium bromide. The most common events were constipation (12/24), of which 11 were mild and one was severe, and thickened secretions (10/24) of which 9 were mild and one was moderate.

Table 4-21 Non-serious adverse events by severity

Event	Severity	Total	
		Events n	Patients[1] n (%)
Choking events, stringy secretions, episode of bleeding from ?oesophogostomy	Mild	0	0 (0.0%)
	Moderate	1	1 (2.6%)
	Severe	0	0 (0.0%)
Constipation	Mild	11	11 (28.2%)
	Moderate	0	0 (0.0%)
	Severe	1	1 (2.6%)
Increased thirst / dry mouth	Mild	1	1 (2.6%)
	Moderate	0	0 (0.0%)
	Severe	0	0 (0.0%)
Thick secretions	Mild	9	8 (20.5%)
	Moderate	1	1 (2.6%)
	Severe	0	0 (0.0%)
Total	Mild	21	16 (41.0%)
	Moderate	2	2 (5.1%)
	Severe	1	1 (2.6%)

Lovardi et al., 2022

Side effects occurred in about 5%. The authors discuss that this limited side effect occurrence could be related to the young age of patients.

Papandreou et al., 2024

Caregivers were instructed to report any side effects to the clinical care team, whenever these occurred, and also specifically asked for their presence or absence in each follow-up appointment. A total of 237 patients were initiated on enteral anticholinergic treatments (n = 150 on glycopyrronium and n = 87 on trihexyphenidyl). According to the paper, a similar profile of side effects was reported in both, namely, constipation (n = 42/237 [17.7%]), urinary retention (14/237 [5.9%]), insomnia (32/237 [13.5%]), and excitation or irritability (21/237 [8.8%]). Oral anticholinergics led to a worsening of constipation, urinary retention, and sleep disturbance, although to a lesser degree, and these effects were generally managed by decreasing the dose rather than stopping medication. It is not possibly to discern which side effects related to glycopyrronium treatment, the age of the child or further information on how AEs were captured or evaluated.

Assessors comment

It is highly relevant to assess how the AEs were captured in this population, as even healthy children aged <3 years old cannot be instructed to systematically report AEs. In the given population this is complicated further, as children with severe, chronic neurological disability often have speech or cognitive disabilities, making it impossible or difficult for them to communicate AEs. Likewise, the

population has several co-morbidities and physical disabilities, e.g. reliance on tracheostomies, gastrostomies or epilepsy. Thus, this population is likely to report a high number of AEs that may be unrelated to treatment, but they are also more vulnerable to effects of anticholinergic treatment. In this context placebo-controlled, blinded studies with prospective, systematic reporting of AEs is most optimal. Instruction of care-givers and inclusion of diaries or scores to systematically capture AEs is important.

SALIVA is double-blinded and a placebo group is included. No diaries or questionnaires were used, but AEs were recorded at several trial visits and caregivers were instructed in reporting of AEs. The study design is acceptable to assess AEs in a population of children aged 3 years and above with chronic neurological disease.

In the PRO-GLY-005 study AEs are retrospectively evaluated in medical charts, and AEs were not systematically captured with the same rigour as they would be in a clinical trial. There is lacking information on how caregivers, patients and medical staff handled reporting of AEs. Only AEs deemed possible, probable or definite by the investigator were included in the submission documents, and no placebo group was included, making independent assessment of the AE profile difficult.

Lovardi (2022) provides insufficient details relating to the nature, capture and evaluation of AEs. There is no placebo-group.

The Papandreou (2024) study also does not include a placebo group, and while it does provide detailed information about more systematic capturing of AEs, it is not possible to assess the safety profile specifically in patients treated with glycopyrronium bromide aged 2-3 years old, since no details on age groups were provided.

The non-serious AEs reported in PRO-GLY-005 are primarily anticholinergic in nature, as is also seen in the SALIVA study, and reflected by the PI. This is in line with the fact that only adverse events considered possible, probable or definite related by the investigator were captured in PRO-GLY-005. PRO-GLY-005 reports potentially treatment-related, non-serious AEs in 48.7% of patients (n = 19), which is similar to the SALIVA study (50% TREA in the glycopyrronium bromide group), although direct comparison is difficult due to methodological differences. Constipation and dry mouth are common in the SALIVA study (20.5% and 6.8% respectively in glycopyrronium bromide group), and in the PRO-GLY-005 study (28.5% and 2.6% respectively). This is in line with the SmPC where dry mouth and constipation are both reported as very common (≥1/10).

However, the diversity of AEs reported in PRO-GLY-005 is limited compared to SALIVA, e.g. PRO-GLY-005 does not include mention of seizures/worsening in epilepsy, behavioural changes or urinary system AEs. The PRO-GLY-005 study primarily reports AEs related to respiratory disease with thickening of secretions/stringy secretions and choking events occurring in >25% of patients. This safety profile is not consistent with the SALIVA study. The differences could be related to methodological differences in how AEs are captured, but could also be related to differences in the populations studied (e.g. lower age, differences in co-morbidities or concomitant medications). It is not possible to disentangle the safety profile in the proposed age group (2-3 years old) and the applicant is requested to present data on AEs in a tabulated format, across studies, comparing children aged 2-3 years old with those aged 3 years and older. Any differences should be addressed, and when relevant, a discussion of the impact on benefit/risk should be included **(MO).**

In the SALIVA study AEs were reduced after the titration phase (27.4% after titration vs. 61.4% during titration of Sialanar®). It is likely that dose titration can reduce AEs. PRO-GLY-005, Lovardi (2022) and Papandreou (2024) do not provide details about this dose/response aspect in children aged 2-3 years old, and it is not further discussed by the applicant how this may influence the safety profile of

glycopyrronium bromide in this age group. If possible, data should be presented from PRO-GLY-005 and this aspect discussed **(OC).**

Papandreou (2024) cannot be further assessed as it is unclear if AEs reported occurred in the relevant population. Lovardi reports significantly fewer AEs (5%), of unknown nature, this difference is likely related to methodological differences.

In conclusion, there are many deficiencies in the AE reporting from the different studies submitted Only summary tables were presented without any correlations, therefore it cannot be deduced e.g. which AEs led to discontinuation (9 of 16 patients), if there is any correlation between dose, duration of treatment, age and AEs, or if there could be any impact of concomitant medication (used for treatment of sialorrhea or other conditions).The Applicant should discuss how it is possible to disentangle the safety profile specifically in the proposed age group (2-3 years old) to support the extension of indication. The MAH's approach to provide only AEs which are assessed as related to the study treatment is not supported. The AE profile in PRO-GLY-005 is not as diverse as in the SALIVA study, which could be related to this way of reporting or assessing AEs. This methodological approach hampers the independent assessment of safety data.

The overall safety data should be submitted, or the applicant should justify that AEs, which were deemed unrelated to the study drug by the investigator in PRO-GLY-005, were not included. In addition, the Applicant is requested to present data on AEs in a tabulated format, across studies, comparing children aged 2-3 years old with those aged 3 years and older. Any differences should be addressed, and when relevant, a discussion of the impact on benefit/risk should be included. Potential amendments to section 4.8 should also be discussed **(MO).**

Serious adverse event/deaths/other significant events

SALIVA

No deaths were reported during the blind and OLSE phases. In total 12 patients reported at least one SAE during the whole study.

During the blind phase 7 patients reported at least one SAE (6 in the glycopyrronium bromide group (13.6%), 1 in placebo group (2.3%)). Of the 6 patients in the glycopyrronium group 3 had a mild SAE, 2 had a moderate and 1 a severe SAE. The SAE in the placebo group was moderate. One patient experienced a treatment-related SAE in the glycopyrronium bromide group (abdominal pain and constipation). The patient was hospitalized and recovered, the severity of the AE was moderate. Five patients in the glycopyrronium bromide group experienced unrelated SAEs (colitis, influenza, infection, decreased appetite, diabetes mellitus, seizure (n = 1 for all)) and one patient in the placebo group (pneumonia).

During the OLSE 2 additional, non-related SAEs were reported in the ex-glycopyrronium bromide group including pyelonephritis (n = 1), epilepsy (n = 1) and 3 in the ex-placebo group including pyrexia (n = 1), urinary tract infection (n = 1) and epilepsy (n=1). In those patients who had been initially treated with glycopyrronium bromide 2 (5.4%) patients experienced one SAE. In those patients initially treated with placebo 3 (8.1%) experienced one SAE. None were considered treatment related.

Assessors comment

SAE are more common in the treatment arm than the placebo arm (13.6% vs. 2.3%). SAEs increase in the ex-placebo arm after initiation of the OLSE phase (8.1% in ex-placebo group). However, only 1 SAE is considered related to the study drug. Narratives for all SAE are provided with some detail about the event. The details of why the investigator did not consider several SAEs related to the study drug

are not discussed or clarified even though several SAEs occur early on in treatment, e.g. during titration, and could be related to anticholinergic effects. The reported treatment-related adverse events (TRAEs) are generally in accordance with the approved PI, only epilepsy (4.5% in GYP arm vs 0% in placebo arm) is not listed. Three SAEs, occurring during the blinded phase, were due to convulsions/epilepsy (IDs: [redacted]) in the period immediately following titration of Sialanar® to a high dose. They are deemed unrelated to treatment by the investigator, but this is not further discussed or justified. In an observational study, Reid (2019), which is briefly mentioned in the clinical overview, worsening of seizures (in 4/62, 6.5%) are also reported – with a major impact on the family, according to caregivers. Epilepsy is not reported in PRO-GLY-005. Among neurological disorders associated to sialorrhea in the SALIVA cohort were cerebral palsy (Sialanar group: 43.2%, placebo group: 55.8%) and epilepsy 32.2% of patients (Sialanar group: 31.8%, placebo group: 32.6%). Thus, these cases could be linked to these neurological disorders, however, the discrepancy warrants further discussion. The applicant should discuss this potential, new safety signal, and consider if it should be included in the SmPC **(OC).**

Real world evidence (PRO-GLY-005)

8 SAE were reported by 6/39 (15.4%) patients included in the study. 7 of the 8 SAE were serious including respiratory arrest (n = 2, 5.1% of patients), thick secretions (n = 2, 5.1% of patients), thickened secretions during acute respiratory infection (n = 1, 2.6% of patients), tracheostomy tube blockage/change (n = 2, 2.6% of patients). In 7.7% of patients a SAE was classed as life-threatening, and in 7.7% it resulted in prolongation of hospitalization. One death was reported, but this was reported as unrelated to glycopyrronium treatment. Adverse events were only included if they were found possibly, probably or definitely related to glycopyrronium bromide, but no further details are given. SAEs deemed unrelated to glycopyrronium bromide were not reported.

Table 4-23 Serious adverse events by severity

Event	Severity	Total	
		Events n	Patients[1] n (%)
Respiratory arrest	Mild	0	0 (0.0%)
	Moderate	0	0 (0.0%)
	Severe	2	2 (5.1%)
Thick secretions	Mild	0	0 (0.0%)
	Moderate	0	0 (0.0%)
	Severe	2	2 (5.1%)
Thickened secretions during acute respiratory infection	Mild	0	0 (0.0%)
	Moderate	0	0 (0.0%)
	Severe	1	1 (2.6%)
Tracheostomy tube blockage/change	Mild	0	0 (0.0%)
	Moderate	1	1 (2.6%)
	Severe	2	1 (2.6%)
Total	Mild	0	0 (0.0%)
	Moderate	1	1 (2.6%)
	Severe	7	5 (12.8%)

Table 4-24 Summary of serious adverse events by serious criteria

Serious criteria	Total	
	Events n	Patients n (%)
Death	0	0 (0.0%)
Life-threatening	5	3 (7.7%)
Required hospitalisation	0	0 (0.0%)
Prolonged existing hospitalisation	3	3 (7.7%)
Resulted in persistent or significant disability or incapacity	0	0 (0.0%)
Congenital anomaly or birth defect	0	0 (0.0%)

Lovardi et al., 2022

Neither the occurrence of SAEs, nor the age or treatment group in which they may have occurred, can be discerned from the data presented.

Papandreou et al., 2024

Neither the occurrence of SAEs, nor the age or treatment group in which they may have occurred, can be discerned from the data presented.

Assessors comment

The treatment-related SAE in the SALIVA study (constipation, abdominal pain) is an unwanted, anticholinergic effect of the drug. SAEs are more frequent in patients receiving glycopyrronium bromide, but only one SAE was found to be treatment-related. In several cases it was not clear why the investigator found the SAE unrelated to the study drug.

The PRO-GLY-005 study included only those SAEs possibly, probably or definitely related to glycopyrronium bromide. 15.4% experienced a SAE, of these 87.5% (7/8) were severe and all were related to the respiratory system. 7.7% of all included patients experienced a life-threatening SAE. Pulmonary and respiratory tract side effects are described in both SALIVA and the SmPC for Sialanar®, as well as in Zeller 2012b study and the physiological mechanism is plausible (e.g. thickened secretions). In the Sialanar EPAR (2016) it is evident that 10% in the OLSE phase (Zeller 2012b) had a SAE, none of the treatment-related SAEs affected the respiratory system. The severity of the SAEs, and the close relation to the respiratory system, is not similar to the observations made in older children in the SALIVA study or in the Zeller 2012b study. As there are no further details (narratives) on these events – and no detailed discussion about the impact on the benefit-risk profile – it is not possible to make an independent assessment of the significance to benefit-risk in this population. The MAH must provide details of these SAEs (narratives, including e.g. age of the child, dosage used, timing, actions taken, other co-morbidities, medications etc.) along with a discussion and justification on the implications to benefit-risk **(MO).**

There was one death in PRO-GLY-005, this was considered unrelated to glycopyrronium bromide, without further details reported. Evidently, several children had conditions associated with a high mortality rate (e.g. spinal muscular atrophy), and considering the length of follow-up, 1 death is not surprising in this cohort. Nevertheless, and especially in the light of the many severe SAEs, the circumstances must be described in a narrative, and the MAH should justify why this death was not considered related to glycopyrronium **(MO).**

The Lovardi (2022) and Papandreou (2024) study cannot be used to assess SAEs as the data is currently presented in the application. The Applicant is requested to provide additional data from these studies if this is available **(OC).**

Laboratory findings

SALIVA:

Clinical laboratory parameters were not systematically monitored in children during the study. There were no marked haematological or other laboratory abnormalities reported (blind phase and OLSE phase) and no abnormal laboratory values were reported as AEs during the study follow-up. Pregnancy tests were performed at baseline when patients were included, and if appropriate at D84, and did not identify any issues.

Real-world evidence (PRO-GLY-005): No data provided.

Lovardi et al., 2022: No data provided.

Papandreou et al., 2024: No data provided.

Safety in special populations

Not discussed.

Safety related to drug-drug interactions and other interactions

Not applicable.

Discontinuation due to adverse events

SALIVA:

Adverse events were the most common reason for discontinuation of study treatment. Treatment-related adverse events led to discontinuation of study treatment in seven patients (15.9%) in the 320 mcg/mL glycopyrronium group: abdominal pain and constipation (one patient, considered a serious adverse event), vomiting and drug intolerance (one patient), flushing and nervousness (one patient), seizure, vomiting, visual impairment, and decreased appetite (one patient each). Two adverse events led to discontinuation of treatment in two patients (4.7%) in the placebo group: fatigue and salivary hypersecretion.

Adverse events leading to treatment discontinuation (blind phase):

		Sialanar® (N=44)	Placebo (N=43)	FAS Total (N=87)
Study treatment discontinuation within 84 days	Yes	7 (15.9%)	4 (9.3%)	11 (12.6%)
If yes,				
time (days) from prescription to last intake	Mean (± SD)	25.6 (± 22.6)	55.3 (± 32.6)	36.4 (± 29.2)
	Median	19	55	27
	Q1-Q3	4-39	27-83.5	15-67
	Min-Max	3-67	27-84	3-84*
time from prescription to last intake of study treatment (classes)	< 28 days	4 (57.1%)	2 (50%)	6 (54.5%)
	[28-84] days	3 (42.9%)	2 (50%)	5 (45.5%)
reason(s) for withdrawal	Adverse event	7 (100%)	2 (50%)	9 (81.8%)
	Insufficient efficacy	0 (0%)	1 (25%)	1 (9.1%)
	Withdrawal of consent	0 (0%)	2 (50%)	2 (18.2%)
last taken dosage of study treatment (mL)	Mean (± SD)	1.7 (± 1.1)	4.2 (± 2.3)	2.6 (± 1.9)
	Median	1.4	4.6	1.4
	Q1-Q3	1.2-1.8	2.3-6	1.2-4
	Min-Max	0.8-4	1.4-6	0.8-6

** or open phase switch,*

In the OLSE phase 6 additional patients discontinued due to AEs. This included epilepsy (n=1), aggression, agitation and faecoloma (n = 1), diarrhea (n=1) and rhinitis and impetigo (n = 1) in the ex-placebo group. In the ex-Sialanar group this included diarrhea (n=1) and anxiety (n=1, 2 episodes). In those patients who had been initially treated with glycopyrronium bromide 2 (5.4%) had at least one TRAE leading to treatment discontinuation. In those patients initially treated with placebo 4 (10.8%) patients had at least one TRAE leading to treatment discontinuation.

Real world evidence (PRO-GLY-005):

16 children (41%) discontinued glycopyrronium bromide during the evaluation period. The reasons for discontinuation, including those not related to glycopyrronium bromide treatment, are shown below. The main reason for discontinuation in 9/39 children (23% of the cohort, 56.3% of all discontinuations) was an adverse event related to glycopyrronium. The reported death was not found to be related to glycopyrronium bromide although no further details are available.

4.5.4 Premature discontinuation of glycopyrronium bromide

Table 4-13 Premature discontinuation of glycopyrronium bromide

	Total n (%)
Discontinued glycopyrronium bromide: n (%)	16 (41.0%)
Reasons for discontinuing[1]:	
Related to adverse event	9 (56.3%)
Lack of efficacy	0 (0.0%)
Adenovirus	1 (6.3%)
Airvo	1 (6.3%)
Death	1 (6.3%)
Increased Work of breathing	1 (6.3%)
Lack of compliance with medication	1 (6.3%)
Not specified	2 (12.5%)
Symptoms improved	1 (6.3%)
Trial of glyco	1 (6.3%)
Ventilated	1 (6.3%)

[1] The 1st discontinuation of glycopyrronium bromide has been considered in this table.

Lovardi et al., 2022:

During the follow-up period glycopyrronium was discontinued in a total of 4/18 (22.2%) patients due to lack of efficacy, parental decision or adverse effects. One patient stopped treatment soon after the first month for lack of efficacy. In two patients' treatment was discontinued after 6 months after it was decided to perform salivary duct ligation. In one patient, treatment was discontinued after 9 months for urinary retention that had no clear relationship with glycopyrronium bromide administration. No further details are given.

Papandreou et al., 2024:

Overall, 26 of the 237 patients (11%) stopped enterally administered anticholinergic treatments because of side effects within 1 year. In the rest, the perceived benefit outweighed concerns, particularly when the dose was decreased. In total, after the start date enteral anticholinergic treatments were continued in 186 of 237 patients (78.5%) at 6 months and 160 of 237 (67.5%) at 1 year. It is unclear how many of the n = 150 receiving glycopyrronium bromide discontinued therapy due to AEs.

Assessors comments

In SALIVA, discontinuation of treatment due to AEs occurred more frequently in the glycopyrronium bromide group compared to placebo (15.9% versus 4.7%). In the PRO-GLY-005 study of children aged <36 months the number of discontinuations due to AEs was higher (23%). In Lovardi (2022) 22.2% (n=4) discontinued treatment. It is unclear how many of these discontinuations were related to AEs, as switch to another treatment in 2 children (salivary duct ligation) could be chosen either due to lack of or insufficient efficacy of the drug or due to unacceptable AEs. The Papandreou (2024) study does not include specific details relating to discontinuation of glycopyrronium bromide. It is recognized that treatment of sialorrhea is often trial/error, and that tolerability may vary depending between individuals. The presented data for discontinuation rates are acceptable.

Post marketing experience

In the years since the launch of Sialanar®, 25% (140/577 enquiries) of all requests from clinicians to the Applicant's medical department have been for evidence and dosing information for children under 3 years of age. There are no in-house data from the company safety database presented by the applicant.

Assessors comment

Sialanar® has been marketed in the EU since 2016. The applicant does not include any post-marketing data from their own safety database or from the EUDRA Vigilance database (EVDAS). However, in the EPAR (2016) data from both are mentioned. The applicant is requested to include safety data from these two databases, specifically related to children aged 2-3 years old. This data should be presented as pooled safety data, in tables when possible, and relevant supplementary information (e.g. narratives as available) should also be included. The applicant should clearly compare the differences across relevant age groups if off-label use in patients <36 months has been reported (e.g. < 36 months versus > 36 months) e.g. in a table **(OC).**

3.5.4. Discussion on clinical safety

Glycopyrronium bromide has been approved for sialorrhea in children aged 3 years and above with chronic neurological disease. The PIP has established an unmet need for this medication in children as young as 2 years old. While the general safety profile of anticholinergic drugs is well understood, the CHMP found that this could not be extrapolated to this population (below 3 years) due to medical complexity.

The safety data presented in support of this application is based on 3 studies including children below 3 years of age with chronic neurological disease; PRO-GLY-005, Lovardi (2022) and Papandreou (2024). Median follow-up in all three studies was >12 months. The two latter articles are of limited value, in the context of a safety assessment, due to lack of data and methodological shortcomings. From a safety point of view, the main problem is the limited exposure in the proposed age range (2-3 years old), methodological short-comings and a lack of detailed reporting, limiting the ability to independently assess the safety profile, with important implications for benefit-risk in the sought indication.

The number of children aged 2-3 years old receiving glycopyrronium is not clear. Papandreou (2024) does not describe the age of patients receiving glycopyrronium bromide. PRO-GLY-005 and Lovardi (2022) include a substantial number of children aged 0-24 months, without providing safety data stratified by age. Especially in children aged 0-12 months old the safety profile is likely different due to immaturity. Pooled safety data is not provided in a format that allows assessment of the safety profile in the approved indication (children with chronic neurological disease >3 years old) versus the proposed indication (children with chronic neurological disease aged 2-3 years old). The data does not include any systematic laboratory testing, ECGs or evaluation of growth. In pediatric populations extrapolation can be acceptable, but in this case, the intended population is medically complex. Previously, the CHMP did not find it appropriate to extrapolate from data collected in older children or adults with sialorrhea. In the current application, extrapolation is not discussed or justified by the applicant, and the proposed indication is only supported by the above-mentioned data.

An important methodological shortcoming is the capture and recording of the AEs and SAEs. Young children with severe, chronic neurological disabilities cannot report AEs, and caregivers may struggle to provide detailed information on the nature of observed AEs. Likewise, the population has several co-morbidities and a high number of AEs is expected. In this context, placebo-controlled, blinded studies

with prospective, systematic reporting of AEs is optimal. Instruction of caregivers and inclusion of diaries or scores to systematically capture AEs is encouraged. The safety data supporting this extension of indication is mainly based on PRO-GLY-005, a retrospective study in which AEs were likely not captured with the same rigour as in a controlled trial. Only AEs deemed possibly, probably or definitely related to treatment was included in the report, and there was no placebo group. Following this, the AEs reported in PRO-GLY-005 are primarily anticholinergic in nature as is also seen in the SALIVA study. PRO-GLY-005 reports potentially treatment-related, non-serious AEs in 48.7% of patients, which is similar to the SALIVA study (50% TREA in the glycopyrronium bromide group). The diversity of the AEs reported in PRO-GLY-005 is limited, compared to SALIVA, and primarily related to the respiratory system. These differences could be related to methodological short-comings in how AEs are captured in PRO-GLY-005, but could also be related to differences in the populations studied (e.g. lower age, differences in co-morbidities or concomitant medications).

The PRO-GLY-005 study included only SAEs possibly, probably or definitely related to glycopyrronium bromide. 15.4% experienced a SAE, of these 87.5% (7/8) were severe and all were related to the respiratory system. 7.7% of all included patients experienced a life-threatening SAE. Pulmonary and respiratory tract side effects are described in both SALIVA and the SmPC for Sialanar®, as well as in pivotal Zeller 2012b study, and the physiological mechanism is plausible (e.g. thickened secretions). However, the severity of the SAEs, and the close relation to the respiratory system, is not similar to the observations made in older children (SALIVA, Zeller 2012b). There was one death in PRO-GLY-005, this was considered unrelated to glycopyrronium bromide, without further details reported. Without narratives describing these events, it is not possible to make an independent assessment of the safety profile in the proposed indication. Before benefit/risk could potentially be considered positive the applicant must document these circumstances. The applicant should justify whether certain populations have an increased risk of AEs/SAEs (e.g. young children, children with severe respiratory co-morbidities or respiratory tract infections). If certain populations at risk can be identified from analysis of the data, the information must be included in the SmPC.

The PRO-GLY-005 analysis is considered potentially the most useful source to support the safety evaluation in extension of the indication. In its current form, data from Lovardi (2022) is only considered supportive for evaluation of safety, while Papanderou (2024) cannot be accepted as supportive of safety in the pediatric subgroup (2-3 years of age). In conclusion, many deficiencies are identified in the submitted data. It has not been possible to evaluate the safety profile of Sialanar in the sought indication (2-3 years of age) from the data presented. It is acknowledged that the details of the data may not be readily accessible and that collection and evaluation of AEs in children aged 2-3 years old with neurological co-morbidities is difficult. However, the Applicant has not provided evidence that it is possible to bridge the safety from the approved indication to the sought indication. This is a major concern **(MO)**.

Additional expert consultations

N/A

Assessment of paediatric data on clinical safety

N/A

3.5.5. Conclusions on clinical safety

Overall, the presented safety data are not considered sufficient to evaluate the safety profile of Sialanar® in the proposed age group of 2-3 years. No safety data from controlled clinical trials are presented, and utility of the currently presented data, including the insufficiently utilized potential of the observational, retrospective data from PRO-GLY-005, is questionable. A critical shortcoming is the lack of details for the proposed age group. In addition, there is limited data on exposure and lack of details relating to potentially severe, life-threatening safety events in the proposed age group. This is a major concern.

4. Risk management plan

The MAH submitted an updated RMP version with this application. The (main) proposed RMP changes were the following:

Rationale for submitting an updated RMP: Approval of Type II variation to modify the approved therapeutic indication to include a new indication/population. The current application is for a change in the lower age limit from 3 years to 2 years.

Summary of significant changes in this RMP:

Change of indication for a lower age of 2 years. Addition of dosing information for a child aged 2 years (weight range 8 to 12 kg) with and without decreased renal function.

The section SVII.2 New safety concerns and reclassification with a submission of an updated RMP, under heading Off label use in patients below the age of 3 years due to the higher susceptibility to adverse effects is supplemented with the following explanatory note: "The current application is for a change in the lower age limit from 3 years to 2 years. Usage data has been presented demonstrating the safe and effective use of glycopyrronium bromide in children between 2 and 3 years of age. As previously noted, the use in children below 3 was not indicated and would therefore be considered off-label use, therefore this risk was no longer considered an important safety concern. In light of the revised age range, the use in children below 2 is therefore not indicated and would therefore be considered off-label use, therefore this risk is no longer considered an important safety concern."

Rapporteur' s assessment comment:

Section SVII.1 *Identification of safety concerns in the initial RMP submission* is expected to be submitted only for initial marketing authorisation applications, "locked" and not change after the approval of the initial RMP. However, in the submitted RMP version 4.1 in the section SVII.1 the subsection SVII.1.2. *Risks considered important for inclusion in the list of safety concerns in the RMP* is changed as follows: "**Important Identified Risk: Off label use in patients below the age of 2 ~~3~~ years due to the higher susceptibility to adverse effects.** Risk-benefit impact: Sialanar is not recommended in children below the age of 2 ~~3~~ years since there is very limited data on the efficacy and safety of glycopyrronium in this age group, and younger children will be more susceptible to adverse effects."

The MAH is asked to follow the recommendation included in the "Guidance on the format of the risk management plan (RMP) in the EU – in integrated format", Rev.2.0.1 accompanying GVP Module V Rev.2 and correct the subsection SVII.1.2. *Risks considered important for inclusion in the list of safety concerns in the RMP* (this section is expected to be submitted only for initial marketing authorisation applications, "locked" and not change after the approval of the initial RMP) to be in line with the guidance. **(OC)**

The RMP for Sialanar should be further revised taking into account the outcome of the further discussions regarding issues outlined in the MO and OC by the CHMP assessor. **(OC)**

4.1. Overall conclusion on the RMP

The changes to the RMP could be acceptable provided an updated RMP and satisfactory responses to the request for supplementary information in section 5 are submitted.

The MAH is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

5. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2 and 4.4 of the SmPC are being updated to include children aged 2-3 years. The Package Leaflet (PL) is updated accordingly.

6. Benefit-Risk Balance

6.1. Therapeutic Context

6.1.1. Disease or condition

Sialorrhea or drooling is the unintentional loss of saliva from the mouth and is a normal phenomenon in infancy. Drooling is usually classed as normal in children up to 4 years of age. However, it is recognised that a proportion of children below 4 years of age suffer from severe sialorrhoea (chronic pathological drooling), usually associated with a chronic neurological condition. A substantial proportion of children with neurological disorders exhibit pathological drooling. The overall prevalence of significant chronic pathological drooling (sialorrhoea) in children is estimated at up to 0.6% (Fairhurst 2011). However, sialorrhoea is significantly more prevalent in neurologically impaired children, including those with cerebral palsy (CP), the most common motor disability of childhood. Estimates of the prevalence of sialorrhoea in these populations vary from 10% to 37%, but may be even higher in some subgroups, especially those with quadriplegic CP (Fairhurst 2011). The clinical need has been determined to be from 2 years of age by the PDCO.

6.1.2. Available therapies and unmet medical need

In terms of oral anticholinergic treatment, glycopyrronium bromide (Sialanar) is the only treatment licensed throughout Europe for children from 3 to 17 years of age. Botulinum toxin A (BTX-A, (Xeomin) is licensed for the symptomatic treatment of chronic sialorrhea due to neurological/neurodevelopmental disorders in children and adolescents aged 2 to 17 years and weighing $\geq$ 12 kg, however that is administered as an injection. Other treatments that are used for severe sialorrhoea include off-label treatment with glycopyrronium bromide, use of hyoscine patches and trihexyphenidylbenzhexol.

6.1.3. Main clinical studies

To support this extension of indication, the MAH relies on existing pharmacokinetic data (Rautakorpi (1994)), a double-blind, placebo-controlled, randomised clinical trial conducted by the MAH (SALIVA

study), a Cohort study (Papandreou et al. (2024)), Real World Data interim analysis (PRO/GLY/005) and Case series (Lovardi et al. (2022)).

6.2. Favourable effects

A significant median change at D84 from baseline was seen for the primary endpoint DIS-F with Sialanar compared to Placebo [Q1, Q3]; (−29.5 [−44.5, 0] vs −1 [−16, 5]; p < 0.001) was seen in the SALIVA study. The change for the Sialanar treatment arm is considered clinically relevant with a minimal clinical important difference of 13.6 points. However, the SALIVA study **did not** include the age group (children aged 2-3 years) applied for in this extension of indication variation.

In Lovardi et al. 2022, the mean DIS at time 0 was 89 (range 81–100) and after 1 month of treatment was 61 (range 43–78); the difference was statistically significant (P < 0.001). The change is considered clinically relevant and was similar to the median change reported in the SALIVA study. Lovardi et al. 2022 is a single arm prospective case study in children under 3 years of age with medical complexity receiving Glycopyrronium bromide for treatment of drooling.

In the retrospective study PRO/GLY/005 a population of patients relevant to the proposed variation (children aged 2-3 years) was included, hence it may be possible to obtain relevant information regarding the efficacy and safety of glycopyrronium bromide for the proposed target population.

The data submitted to inform on the pharmacokinetics of glycopyrronium in the paediatric population, is the same as in the initial PUMA. It is a study by Rautakorpi 1994 evaluating a single dose of IV glycopyrronium in 26 children undergoing minor surgery. Data are limited, but the PK of glycopyrronium does not seem to differ from those aged 3 years and above. The low and variable oral absorption defines the need for a slow titration phase based on the patient's weight as recommended in the SmPC. However, the data is not considered sufficient to use as a PK bridge.

6.3. Uncertainties and limitations about favourable effects

The SALIVA study did not include children in the applied age-group (2-3 years) but serves as a comparator for the other studies for the primary endpoint. Due to uncertainties regarding children included in the age-group 2-3 years, the data from the Papandreou 2024 study is not considered to support the efficacy in children aged 2-3 years, unless the MAH can provide data in the sought age-group. **(MO)** The PRO/GLY/005 study did not provide any efficacy endpoint data, but the data include the use of Glycopyrronium bromide in the applied age-group. The Lovardi 2022 study include the use of Glycopyrronium bromide in the applied age-group and even though the study has limitations due to the study design (case series), the result may support the efficacy of Glycopyrronium bromide in children aged 2-3 years with chronic neurological disorders.

There are no RCTs to support the efficacy in 2-3 year old children. Only RWD like observational cohort studies and case series have been submitted that include data on children below 3 years of age. However, the data that the decision on benefit-risk is to be based on are liable to confounding and bias. This needs to be considered in the overall evaluation.

The treatment used in Lovardi et al. (2022) was glycopyrronium bromide 0.5 mg tablet and treatment used in PRO/GLY/005 was enteral glycopyrronium bromide, not further detailed in the study report. Hence, the formulations used and the impact of the different formulations/excipients on the pharmacokinetics are uncertain. **(MO)**

Overall, the design of the studies to support the efficacy of glycopyrronium bromide in children aged 2-3 years are hampered by the nature of real-world data and literature data, with single arm trial design,

not blinded or randomized and with sparse information on eligibility criteria. Further, the different study designs, different statistical methods, endpoints and different formulations and doses, makes it difficult to compare the results between the studies.

6.4. Unfavourable effects

Retrospective data on AEs in children aged < 3 years old are presented in PRO-GLY-005 and are primarily anticholinergic in nature. Constipation and dry mouth are common (28.5% and 2.6% respectively). PRO-GLY-005 reports treatment-related, non-serious AEs in 48.7% of patients. This is in line with previous, placebo-controlled studies in children aged 3 years and above (SALIVA), the expected effects of anticholinergic drugs, and with the SmPC.

However, the diversity of AEs reported in PRO-GLY-005 is limited compared to SALIVA, e.g. PRO-GLY-005 does not include mention of seizures/worsening in epilepsy, behavioural changes or urinary system AEs. The PRO-GLY-005 study primarily reports AEs related to respiratory disease with thickening of secretions/stringy secretions and choking events occurring in >25% of patients. This safety profile is not consistent with the SALIVA study or the SmPC. In PRO-GLY-005 7.7% of children experience life-threatening SAEs. The severity of the SAEs, and the close relation to the respiratory system, is not similar to the observations made in older children in the SALIVA study or in the Zeller 2012b study.

These differences could be related to methodological differences in how AEs are captured but could also be related to differences in the populations studied (e.g. lower age, differences in co-morbidities or concomitant medications). Furthermore, the Applicant did not discuss nor describe the safety profile in the proposed age group (2-3 years old). Therefore, it is not possible to assess if the observed differences are relevant for the proposed age group. A meaningful conclusion on safety in the proposed indication cannot be drawn at the current time **(MO).**

6.5. Uncertainties and limitations about unfavourable effects

The data provided by the Applicant includes two published studies (Papandreou, 2024 and Lovardi, 2022) and real-world evidence (PRO-GLY-005). All three include children with chronic neurological disease and sialorrhea, median follow-up was >12 months. SALIVA is a placebo-controlled, randomized trial in children aged 3 years and older, included in the application to provide comparative data. Several important limitations were identified.

None of the studies provide controlled safety data which is a significant limitation in a vulnerable population of children with severe co-morbidities. A key problem in all three studies is the lack of age stratification. It is not possible to establish how many children in the proposed age group were exposed, how many were exposed long-term (> 12 months) and what the AE profile was. PRO-GLY-005 and Lovardi (2022) include a substantial number of children aged 0-23 months, and especially in children aged 0-12 months old the safety profile is likely different due to immaturity. If a significant number of children aged 0-12 months are included this may skew the safety profile, potentially towards a different or more severe safety profile, than what is actually the case in patients aged 2-3 years old **(MO).**

The methodology for capturing AEs and SAEs is prone to underreporting, particularly in Lovardi (2022) and PRO-GLY-005. Systematic, prospective and controlled capture of AEs is important in populations with limited ability to self-report. In PRO-GLY-005 AEs are retrospectively evaluated in medical charts. There is lacking information on how caregivers, patients and medical staff handled reporting of AEs. Only AEs deemed possible, probable or definite by the investigator were included in the submission

documents, and no placebo group was included, making independent assessment of the AE profile in the proposed age group difficult. Another major concern is the lack of detailed narratives relating to life-threatening SAEs and one death in PRO-GLY-005 **(MO)**.

6.6. Effects Table

No meaningful conclusions on favourable and unfavourable effects can be drawn for the proposed age group.

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

Sialanar is approved for severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders. The clinical need has been determined to be from 2 years of age by the PDCO.

There are no RCTs to support the efficacy in 2-3 year old children. Only RWD, like observational cohort studies and case series, have been submitted that include data on children below 3 years of age. These types of data are liable to confounding and bias. Although the submitted evidence include children below the age of 3 years, the Applicant has not provided data nor discussed the efficacy or safety specifically for this patient population. Although it could be anticipated that efficacy will be the same, it is of major importance that the Applicant address the efficacy in the sought population.

Further, it is uncertain which formulations was used in the RWD and case series and the impact of the different formulations/excipients on the pharmacokinetics are not discussed.

Controlled safety data are not provided, and independent assessment of unfavourable effects in the proposed age group is hampered by methodological concerns and lack of data. The most significant are as follows; the lack of pooled exposure data stratified by age, the deficiencies in the AE reporting (including lack of pooled data stratified by age) and the lack of clinical, supplementary information on SAEs and deaths. All of these limitations have important impact on benefit/risk.

6.7.2. Balance of benefits and risks

The value of the presented efficacy- and safety data, across all three studies (Lovardi, 2022, Papandreou, 2024 and PRO-GLY-005), is hampered by methodological limitations, lack of details and no age stratification. As such a conclusion on efficacy and safety in the proposed age range 2-3 years cannot be made at the current time, which has major implications for the assessment of the benefit/risk.

6.8. Conclusions

The overall B/R of Sialanar in children aged 2 and up to 3 years old with chronic neurological disorders is currently negative.