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ORIGINAL ARTICLE

Glycopyrronium 320 μg/mL in children and adolescents with severe sialorrhoea and neurodisabilities: A randomized, double-blind, placebo-controlled trial

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Abstract

Aim: To investigate the efficacy, safety, and impact on quality of life (QoL) of an oral formulation of 320 μg/mL glycopyrronium designed for children.

Method: A double-blind, placebo-controlled SALIVA (Sialanar plus orAl rehabiLitation against placebo plus oral rehabilitation for chIldren and adolescents with seVere sialorrhoeA and neurodisabilities) trial was conducted. Children (3–17 years) with neurodisabilities and severe sialorrhoea (modified Teachers Drooling Scale ≥6) were randomized to 320 μg/mL glycopyrronium or placebo, in addition to non-pharmacological standard care.

Results: Of 87 participants, 44 were aged 10 years or under and 43 had cerebral palsy. The primary endpoint, change in total Drooling Impact Scale (DIS) score from baseline to day 84, was significantly greater (improved) with 320 μg/mL glycopyrronium versus placebo (median [quartile 1, quartile 3] −29.5 [−44.5, 0] vs −1 [−16, 5]; $p < 0.001$), an effect also observed at day 28 (median −25 vs −2; $p < 0.01$). Significant reduction in bibs/clothes used per day was seen with glycopyrronium versus placebo at day 84 (median −2 vs 0; $p < 0.01$). Glycopyrronium significantly improved DIS items 9 and 10 related to the extent that drooling affects the child's and family's life ($p \leq 0.03$). Adverse events were reported by 77.3% and 69.8% of children with glycopyrronium and placebo respectively; the most common treatment-related adverse event was constipation (20.5% and 16.3%).

Interpretation: The formulation of 320 μg/mL glycopyrronium significantly improved drooling and reduced its impact on QoL, with good tolerability in children with neurodisabilities.

Excessive drooling is common in children with neurodevelopmental disorders, occurring in 40% to 60% of children with cerebral palsy (CP), the leading cause of paediatric motor disability,[1] and is reported to be severe in 15% of cases.[2–4] Severe anterior drooling can lead to skin maceration and dehydration, can adversely affect social interactions and self-esteem, and is known to have a substantial impact on health-related quality of life (QoL).[5–7] Drooling also adds to the care burden of parents/caregivers with practical consequences, including frequent changes of bibs and clothing.[5,6] Posterior drooling can lead to aspiration and recurrent respiratory infections,[4,8] which are a significant cause of mortality. In 349 people with

Abbreviations: DIS, Drooling Impact Scale; DIS-F, Drooling Impact ScaleFrench Edition; QoL, quality of life; SALIVA, Sialanar plus orAl rehabiLitation against placebo plus oral rehabilitation for chIldren and adolescents with seVere sialorrhoeA and neurodisabilities.

CP with available data on cause of death, 58.6% of deaths were attributed to respiratory causes, including 49% to pneumonia at a mean age of 14 years 7 months, and of these, 45% were attributed to aspiration.[9] Respiratory illness is also the most common cause of presentation to the emergency department and of prolonged hospital admissions in children with CP.[10]

Non-pharmacological rehabilitation methods such as intraoral stimulation and oral facial exercises are often used as the first approach, but these are not always successful alone and medical therapy may be necessary.[8,11]

An oral solution of glycopyrronium bromide (1 mg/5 mL) was approved in the USA in 2010 to treat chronic severe drooling associated with neurological conditions in paediatric patients;[12] however, no licensed treatments were available for severe drooling in Europe until 2017. A formulation of 320 μg/mL glycopyrronium, equivalent to 400 μg/mL glycopyrronium bromide (2 mg/5 mL), was granted a licence for the treatment of severe drooling in children with neurological disorders by the European Medicines Agency under the Paediatric Use Marketing Authorisation procedure.[13] Botulinum neurotoxin A was licensed in Europe in 2022. The German S2k guideline for hypersalivation recommends glycopyrronium in children and adolescents, stating its effect can be well titrated and should be administered on a regular basis.[14] The guidelines suggest botulinum neurotoxin as an alternative treatment owing to its long-lasting effect, albeit with prolonged dosage finding for effect in some patients.

Glycopyrronium has a similar side-effect profile to other anticholinergic medications, such as gastrointestinal dysmotility and dry mouth,[8] but owing to its quaternary amine structure it has restricted ability to cross the blood–brain barrier and is therefore associated with reduced central nervous side-effects compared with tertiary amines, such as atropine and scopolamine.[15] Limited trial data are available comparing different anticholinergics; however, glycopyrronium reduced problematic drooling and was associated with better tolerability than other agents in both the open-label Drooling Reduction Intervention trial assessing glycopyrronium 160 μg/mL (glycopyrronium bromide 1 mg/5 mL) and scopolamine[16] and in a real-world study of glycopyrronium (unknown off-label formulation), benzhexol, and scopolamine.[17]

Formulations of glycopyrronium bromide (1 mg/5 mL and 2 mg/5 mL) have relied on bioavailability studies to bridge from existing efficacy and safety studies on a glycopyrronium bromide 1 mg/5 mL solution licensed in the USA.[18,19] However, the European-approved 320 μg/mL glycopyrronium paediatric formulation (2 mg/5 mL) is known to be 25% more bioavailable than a 1 mg/5 mL formulation[13] and, along with its more concentrated solution, results in a 60% lower volume per dose.

The SALIVA (Sialanar plus orAl rehabiLitation against placebo plus oral rehabilitation for chIldren and adolescents with seVere sialorrhoeA and neurodisabilities) trial is the first double-blind trial conducted to measure the efficacy, tolerability, and also QoL in children with neurological disorders receiving 320 μg/mL glycopyrronium for severe drooling.[20]

What this paper adds

- The formulation of 320 μg/mL glycopyrronium significantly improved Drooling Impact Scale score versus placebo at day 84.
- The formulation reduced the impact of drooling on the child's and family's quality of life.
- There were no safety or tolerability concerns with this specific formulation.

Here we report the results of the initial 3-month blinded period.

METHOD

Trial design

The design of the SALIVA trial has been described previously[20] (Figure S1). Briefly, the oral 320 μg/mL glycopyrronium formulation was compared with placebo in a 3-month double-blind, randomized trial (EudraCT 2020–005534-15) conducted in 13 French centres, mostly based in university hospitals, which specialize in treating childhood neurodisabilities or in paediatric otorhinolaryngology. All patients who completed the initial 3-month blinded period were invited to receive 320 μg/mL glycopyrronium in a 6-month open-label study extension, which is ongoing. The protocol was approved by an independent ethics committee and the French Agence Nationale de Sécurité du Médicament.

Trial population

Key eligibility criteria included age between 3 and 17 years old, chronic neurodisabilities (such as CP, Angelman syndrome, Rett syndrome, epilepsy, amyotrophic lateral sclerosis, encephalopathy, and intellectual disability), severe sialorrhoea (defined as ≥6 on the modified Teachers Drooling Scale) and a Drooling Impact Scale (DIS) score ≥ 50. All participants had received ≥3 months of non-pharmacological rehabilitation, based on French regional recommendations,[21] and continued to receive the same regimen during the trial. Children fed orally or by gastrostomy feeding were included. Children were not eligible if they received other recent treatment for drooling, namely scopolamine patches or any other anticholinergic therapy (e.g. atropine and trihexyphenidyl) in the previous 4 weeks, botulinum neurotoxin injection within 6 months, or surgery in the previous 12 months. Investigators considered new and existing patients for possible enrolment and obtained written consent from both parents (or the participant's legally acceptable representative[s] where applicable) before recruitment.

Randomization and intervention

Using an Interactive Web Response System, eligible participants were randomized 1:1 to receive either oral 320 µg/mL glycopyrronium or a matched placebo oral solution, three times daily in a blinded manner for 3 months. The dose of study drug was titrated over a period of up to 4 weeks, consistent with the Summary of Product Characteristics of the licensed drug[13] (Table S1). Outpatient visits took place at day 28 (±2 days) and day 84 (±5 days), while telephone interviews occurred every week during the titration period and at day 56.

Endpoints

The primary endpoint was the change in DIS score from baseline to day 84 using the validated French edition of the DIS (DIS-F).[22] The lowest score is 10 and the maximum possible score is 100, with the higher scores indicating greater severity and impact. The minimally clinically important difference was selected as 13.6 points based on the findings of Reid et al.[23] DIS-F was completed on a paper questionnaire by the investigator in a semi-directed interview with the same parent/carer (where possible) at baseline and during outpatient visits at 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 based on Reid et al.[23]) 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?'). An additional QoL endpoint was change from baseline to day 84 in DISABKIDS score. DISABKIDS is a generic QoL scale designed to assess health-related QoL in children and adolescents with chronic diseases[24] whatever the pathology and the population. Questionnaires include a 37-item version and a short 12-item version for children aged older than 8 years. Higher values indicate better health-related QoL. DISABKIDS-37 parent questionnaires were completed by the same parent/carer (where possible) at baseline, day 28 (±2 days), and day 84 (±5 days). DISABKIDS-12 child questionnaires were completed by the child, where possible, at baseline, day 28 (±2 days), and day 84 (±5 days).

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.

Statistical methods

A sample size of 23 individuals per group was calculated to be required to detect a minimum clinically significant difference of 13.6 points in the mean DIS score with 90% power, assuming a two-sided type 1 error rate of 5% and 13.6 as standard deviation (based on Reid et al.[23]). Allowing for approximately 20% to 30% loss to follow-up, enrolment of 60 children was estimated to be required to evaluate the primary endpoint; however, target enrolment was set at 80 children to compensate for terminations and to enable at least 60 children to continue into the extension period.

The primary endpoint was evaluated in the full analysis set (intention-to-treat population, which included all randomized patients analyzed according to the treatment they were randomized to receive) and in the modified intention-to-treat set (which excluded all patients deemed ineligible after randomization or who did not start study medication). The DIS score measurements at baseline (day 0) were used to replace unavailable DIS scores at day 84 (premature end) considering patients as non-responders. Considering unnormalized distribution of change in DIS score, even with attempted transformation, a non-parametric Mann–Whitney *U* test was used to compare score change between the two treatment groups. Additionally, a non-parametric Wilcoxon signed-rank test was used to assess significant within-group changes over time.

Sensitivity analyses included comparisons of differences (1) for patients with a DIS completed strictly by the same person at days 0 and 84, (2) when an unavailable DIS at day 84 is replaced by the latest available DIS, and (3) in the per-protocol population (all patients who did not violate the terms of the protocol in a way that would affect the study outcome significantly, as determined by the study clinician blinded to study drug assignment).

If the primary endpoint was significant, a hierarchical test sequence was planned for the secondary efficacy endpoints in the following order: proportion of responders at day 84, changes in DIS at day 28, proportion of responders at day 28, proportion of good responders at day 84, changes in bib/clothes per day at day 84, and changes in bib/clothes per day at day 28, with loss of significance resulting in a halt to further statistical analyses. The same analysis methods were used for secondary endpoints as for the primary endpoint, with a X^2 test used for the responder and good responder comparison between the two treatment groups. These responder analyses were also adjusted for baseline DIS score, with logistic regressions.

RESULTS

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 (Figure S2). The randomized population included 42 females (48.3%) and 44 children (50.6%) were aged 10 years or under (range

3 years 5 months–17 years 8 months) (Table 1). Participants commonly had CP (49.4%), epilepsy (32.2%), intellectual disability (29.9%), or other neurological disorders (35.6%), with a high level of physical impact (72.4% were classified in Gross Motor Function Classification System levels III–V). Baseline characteristics were generally well balanced, although there were more patients with 'other neurological disorders' in the 320 μg/mL glycopyrronium group than in the placebo group.

Almost 90% of children had a modified Teachers Drooling Scale score of 8 or 9, indicating profuse drooling. All patients had received oro-motor rehabilitation, with 74.7% of patients still receiving it at baseline (oro-motor rehabilitation, 36.9%; speech therapy, 76.9%; sensory stimulation, 35.4%). Of those children who stopped oro-motor rehabilitation, 40.9% cited insufficient efficacy as the reason. In total, 36.8% of patients had no previous medical treatment for sialorrhoea, 31.0% had received scopolamine patches only, 5.7% had received botulinum neurotoxin injections only, and 20.7% had received scopolamine and botulinum neurotoxin injections (Table 1), with a mean time from the end of the

TABLE 1 Baseline characteristics.

	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)
Other neurological disorder	21 (47.7)	10 (23.3)
Rett syndrome	1 (2.3)	1 (2.3)
Angelman syndrome	0 (0)	1 (2.3)
GMFCS level, *n* (%)		
I	3 (6.8)	2 (4.7)
II	12 (27.3)	7 (16.3)
III	2 (4.5)	6 (14.0)
IV	12 (27.3)	13 (30.2)
V	15 (34.1)	15 (34.9)
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)
Types of rehabilitation followed at baseline, *n* (%)		
Oro-motor rehabilitation	11 (33.3)	13 (40.6)
Speech therapy	27 (81.8)	23 (71.9)
Sensory stimulation	13 (39.4)	10 (31.3)
Other rehabilitation	0 (0)	1 (3.1)
Previous medical treatment for sialorrhoea,[a] *n* (%)		
No previous medical treatment	14 (31.8)	18 (41.9)
Scopolamine only	17 (38.6)	10 (23.3)
Botulinum neurotoxin injection only	2 (4.5)	3 (7.0)
Scopolamine patch and botulinum neurotoxin injection	8 (18.2)	10 (23.3)
Scopolamine patch, botulinum neurotoxin injection and surgery	1 (2.3)	2 (4.7)
Scopolamine injection given orally	1 (2.3)	0
Scopolamine patch plus trihexyphenidyl	1 (2.3)	0

[a]Children were only eligible if they had not received any anticholinergic therapy in the previous 4 weeks, botulinum injection within 6 months, or surgery for drooling in the previous 12 months.

Abbreviations: GMFCS, Gross Motor Function Classification System; Q1, Q3, quartile 1, quartile 3.

other medical treatment to study treatment of more than 2 years (data not shown). The median (quartile 1, quartile 3 [Q1, Q3]) volume of 320 µg/mL glycopyrronium received was 1.1 mL (0.8, 1.4) at the initial dose and 4 mL (3.2, 6) at day 84.

Total DIS scores indicated severe drooling and were similar between the groups at baseline (Table 2). For the primary endpoint, the median (Q1, Q3) change in total DIS score from baseline to day 84 was significantly greater (improvement) with 320 µg/mL glycopyrronium than placebo (−29.5 [−44.5, 0] vs −1 [−16, 5]; $p < 0.001$) (Table 2). 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]; $p < 0.001$) (Table S2). The median change in total DIS score from baseline to day 84 was statistically different within the two groups ($p < 0.001$ for 320 µg/mL glycopyrronium and $p = 0.01$ for placebo).

Improvements in total DIS score were noted early after initiation, with a significant difference observed between 320 µg/mL glycopyrronium and placebo at day 28 (−25 [−43, −0.5] vs −2 [−21, 1]; $p < 0.01$) (Table 2). There were significantly more responders (on the basis of the minimally clinically important difference) and good responders with 320 µg/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

TABLE 2 Primary and secondary efficacy analyses.

DIS score[a]		320 µg/mL glycopyrronium $n = 44$	Placebo $n = 43$	p[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	
	p[c]	<0.001	<0.01	
	Responders[d], *n* (%)	27 (61.4)	12 (27.9)	<0.01
	95% CI	43–79.8	2.5–53.3	
	Good responders[e], *n* (%)	20 (45.5)	8 (18.6)	<0.01
	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 responders[e], *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 X^2 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.

$p < 0.01$). The difference was also significant when adjusted for baseline DIS ($p < 0.01$).

Furthermore, there was a significantly greater reduction in DIS item 3 with 320 µg/mL glycopyrronium versus placebo: the median (Q1, Q3) number of bibs/clothes used per day with 320 µg/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 µg/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 3). For the QoL item related to the extent that the child's dribbling affected the family's life, treatment with 320 µg/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; $p < 0.01$).

The number of parents/caregivers completing the DISABKIDS-37 questionnaire in full was low at day 84 (14 respondents in the 320 µg/mL glycopyrronium group, 21 in the placebo group). Although some dimensions were completed by most parents, such as those related to mental independence and physical limitations (both > 90%), other dimensions had much lower completion rates, such as those related to mental emotion (78%) and physical treatment (64%). In parents who completed the whole DISABKIDS-37 questionnaire, there seemed to be no clear difference between the treatments ($p = 0.87$) (Table 3). The number of children completing the DISABKIDS short questionnaire, either partly or fully, was very low (three or four per group) and precluded statistical analysis of the results.

In total, 61.4% of children reported any adverse event with 320 µg/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 4). Treatment-related adverse events were reported by 50.0% of children with glycopyrronium 320 µg/mL and 34.9% with placebo at day 84. The most frequent treatment-related adverse events were constipation (20.5%), dry mouth (6.8%), and vomiting (6.8%) in the 320 µg/mL glycopyrronium group and constipation (16.3%), diarrhoea (7.0%), and fatigue (7.0%) in the placebo group (Table 5). Adverse events were the most common reason for discontinuation of study treatment (Figure S2). Treatment-related adverse events led to discontinuation of study treatment in seven patients in the 320 µg/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 in the placebo group: fatigue and salivary hypersecretion.

TABLE 3 Quality-of-life analyses.

	320 µg/mL glycopyrronium	Placebo	p[c]
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
DISABKIDS-37 long form (by parents/caregivers)[b]			
	$n = 14$	$n = 21$	
Median (Q1, Q3) total score at baseline	60.8 (52.4, 71.3)	56.6 (49.9, 62.6)	—
Change from baseline to day 84	2.1 (−10.1, 7.6)	−0.1 (−4.2, 8.5)	0.87
DISABKIDS-12 short form (by child)[b]			
	$n = 4$	$n = 3$	
Median (Q1, Q3) total score at baseline	78.1 (69.8, 87.5)	68.8 (54.2, 87.5)	—
Change from baseline to day 84	−6.3 (−14.6, 2.1)	−16.7 (−25.0, −2.1)	—

[a]Higher scores indicate greater severity and impact.

[b]Higher scores indicate better quality of life. Data analyzed for patients with scores at both inclusion and day 84.

[c]Mann–Whitney *U* test.

Abbreviations: DIS, Drooling Impact Scale; Q1, Q3, quartile 1, quartile 3.

TABLE 4 Overview of adverse events by period.

Number (%) experiencing at least one event	Day 0 to day 28		Day 29 to day 84		Day 0 to day 84	
	320 μg/mL glycopyrronium *n* = 44	Placebo *n* = 43	320 μg/mL glycopyrronium *n* = 44	Placebo *n* = 43	320 μg/mL glycopyrronium *n* = 44	Placebo *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)

TABLE 5 Study treatment-related adverse events (occurring in ≥10% in the trial and/or defined as 'very common' [≥1/10] in the Summary of Product Characteristics[13,a]) 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

[a]Adverse events listed in the Summary of Product Characteristics[13] as 'very common': irritability, flushing, nasal congestion (none recorded in the trial), reduced bronchial secretions (none recorded in the trial), dry mouth, constipation, diarrhoea, vomiting, urinary retention.

DISCUSSION

In the first formal comprehensive randomized trial to examine glycopyrronium efficacy and safety alongside its impact on QoL, 320 μg/mL glycopyrronium was effective at improving drooling and reducing the impact of drooling on the child's and family's day-to-day life. The population of patients had baseline DIS scores indicative of severe and profuse problematic sialorrhoea, requiring additional treatment following non-pharmacological standard care, with over half having already tried scopolamine some years previously.

The 320 μg/mL glycopyrronium formulation significantly reduced drooling, using the validated DIS-F. Both the DIS and DIS-F have been used in other drooling studies[16,23] and are the only evaluative tools with responsiveness data that are useful for detecting clinically important changes over time.[25] Furthermore, an evaluation of DIS, modified Teachers Drooling Scale, and the Drooling Severity and Frequency Scale found that although all were effective in the diagnosis of drooling, both for rating its severity and frequency, DIS was the only tool that considered the physical complications of drooling and its impact on QoL.[26]

In the current trial, 320 μg/mL glycopyrronium reduced the impact of drooling in practical terms by decreasing the number of bib and clothing changes by more than two occurrences per day, freeing up time for the carer to focus on other aspects of effective care and reducing related costs (e.g. washing, etc.). In addition, both the children and their families reported improvements in the extent that drooling affected their lives with 320 μg/mL glycopyrronium treatment. Results for individual DIS items were not published for the Drooling Reduction Intervention trial[16] and have not previously been statistically analyzed.

The SALIVA trial also attempted to assess whether an improvement in drooling could be measured in terms of overall QoL using validated DISABKIDS questionnaires designed for children with chronic diseases in general,[24] not necessarily related to neurological impairment; however, interpretation of our results is limited by the very low completion rate. Fewer than half of the parents fully completed the 37-item questionnaire and the low rates of completion of some dimensions suggest there were parts of the DISABKIDS questionnaire that may not have been appropriate for parents and children with the neurological impairments studied in this trial. As only seven children in total completed the 6-item version, no conclusions could be drawn. DISABKIDS was chosen because of its wide age range, but the development of a general QoL scale for children with neurodisabilities aged 3 to 18 years may be warranted.

Anticholinergic treatment is associated with predictable known side-effects. In the current trial, treatment-related adverse events identified as very common (>10%) in the formulation's Summary of Product Characteristics, such as irritability, flushing, dry mouth, vomiting, and urinary retention,[13] occurred at a rate below 10%. Constipation was recorded as a treatment-related adverse event in 20.5% of patients on 320 μg/mL glycopyrronium versus 16.3% on placebo. In a previous 8-week double-blind trial in 38 children with severe drooling, 40% experienced a dry mouth with 160 μg/mL glycopyrronium (1 mg/5 mL glycopyrronium bromide) compared with 11% on placebo, while 30% of children each reported constipation, vomiting, and nasal congestion (rates were 22%, 11%, and 5%, respectively, for placebo).[18] As in other trials with glycopyrronium, adverse events were the most common reason for discontinuation of study treatment.[16,19] The rate of discontinuation due to treatment-related adverse events in the current trial (15.9%) was consistent with the 12-week Drooling Reduction

Intervention trial, where 15.8% discontinued 160 μg/mL glycopyrronium owing to problematic predictable side-effects, whereas 36.2% discontinued scopolamine.[16]

The formulation of 320 μg/mL glycopyrronium evaluated in the SALIVA trial was developed specifically for use in the paediatric population, such that it is palatable, easily and accurately titrated, and has minimal excipients, all of which are appropriate for use in children. Its improved bioavailability versus a 160 μg/mL glycopyrronium liquid[13] results in 60% less volume per milligram dose. The need for a concentrated solution is important for children with CP, particularly when they receive medication orally. For children fed orally, a recent study found that the median dysphagia limit (the upper limit of liquid that can be swallowed in one bolus) was significantly greater for typically developing children (22.0 mL) than for those with CP (7.0 mL) ($p < 0.001$) and differed significantly between Eating and Drinking Ability Classification System levels, ranging from 0.5 mL for level V to 7.0 mL for level I ($p < 0.001$).[27] [Correction added on 9 February 2024 after first online publication: In the preceding sentence, the value of 3.0 mL has been changed to 7.0 mL.]

CONCLUSION

In children with neurodisabilities and severe sialorrhoea, this specifically designed paediatric formulation of 320 μg/mL glycopyrronium significantly improved drooling, reduced its impact on the daily life of the child and their families, and was well tolerated.

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CONFLICT OF INTEREST STATEMENT

PF receives fees from Merz Pharma for providing training sessions. HS and FV are employees of Proveca Ltd. GL has given lectures for Nutricia Clinical Nutrition and Nestlé Health Science. SA has served as consultant or given lectures for Angelini, Biocodex, Eisai, Encoded, Grintherapeutics, Jazz Pharmaceuticals, Neuraxpharm, Orion, Nutricia, Proveca, UCB Pharma, Vitaflo, Xenon, and Zogenix. SA has been an investigator for clinical trials for Eisai, Marinus, Proveca, Takeda, UCB Pharma, and Zogenix. DS is an employee of the contract research organization Kappa Santé. MD and SR have stated that they had no interests that might be perceived as posing a conflict or bias.

DATA AVAILABILITY STATEMENT

The data set analyzed during the current study is not publicly available owing to health data protection but is available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

The following additional material may be found online:
Figure S1: Trial design overview.
Figure S2: CONSORT diagram.
Table S1: Dosing table used in the SALIVA trial.
Table S2: Sensitivity analyses on the primary endpoint.

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Prescribing Information (UK and Republic of Ireland)

Sialanar (400 mcg/ml glycopyrronium bromide, equivalent to 320 mcg/ml glycopyrronium) oral solution. Please refer to the full Summary of Product Characteristics (SmPC) before prescribing.

Active ingredient: 1ml contains 400mcg glycopyrronium bromide (equivalent to 320 micrograms glycopyrronium). **Indication:** Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders. **Dosage:** Start with approximately 12.8 micrograms/kg body weight of glycopyrronium per dose, three times per day. Increase dose weekly until efficacy is balanced with side effects. Titrate to maximum individual dose of 64 mcg/kg body weight glycopyrronium or 6 ml three times a day, whichever is less. Monitor at least 3 monthly for changes in efficacy and/or tolerability and adjust dose if needed. Not for patients less than 3 or over 17 years old as Sialanar is indicated for the paediatric population only. ***Renal impairment:*** Reduce dose by 30%, in mild/moderate renal failure. **Method of Administration:** Oral use only. Dose at least one hour before or two hours after meals or at consistent times with respect to food intake. Avoid high fat food. Flush nasogastric tubes with 10 ml water. **Contraindications:** Hypersensitivity to active substance or excipients; pregnancy and breast-feeding; glaucoma; urinary retention; severe renal impairment/dialysis; history of intestinal obstruction, ulcerative colitis, paralytic ileus, pyloric stenosis; myasthenia gravis; concomitant treatment with potassium chloride solid oral dose or anticholinergic drugs. **Undesirable effects:** Adverse reactions more common with higher doses and prolonged use. In placebo-controlled studies (≥15%) dry mouth, constipation, diarrhoea and vomiting, urinary retention, flushing and nasal congestion. In paediatric literature; *very common:* irritability, reduced bronchial secretions; *common:* upper respiratory tract infection, pneumonia, urinary tract infection, agitation, drowsiness, epistaxis, rash, pyrexia. The Summary of Product Characteristics should be consulted for a full list of side effects. **Special warnings and precautions:** Monitor anticholinergic effects. Carer should stop treatment and seek advice in the event of constipation, urinary retention, pneumonia, allergic reaction, pyrexia, very hot weather or changes in behaviour. For continuous or repeated intermittent treatment, consider benefits and risks on case-by-case basis. Not for mild to moderate sialorrhoea. Use with caution in cardiac disorders; gastro-oesophageal reflux disease; pre-existing constipation or diarrhoea; compromised blood brain barrier; in combination with: antispasmodics, topiramate, sedating antihistamines, neuroleptics/antipsychotics, skeletal muscle relaxants, tricyclic antidepressants and MAOIs, opioids or corticosteroids. Sialanar contains 2.3 mg sodium benzoate (E211) in each ml. Patients require daily dental hygiene and regular dental checks. Thicker secretions may increase risk of respiratory infection and pneumonia. Moderate influence on ability to drive/use machines. **Fertility, pregnancy, and lactation:** Use effective contraception. Contraindicated in pregnancy and breast feeding. **Legal classification:** POM. **Further information available on request from the Marketing Authorisation Holder. Date of last revision of prescribing information:** May 2023.

For the United Kingdom

Marketing Authorisation Holder: Proveca Pharma Ltd. 2 Dublin Landings, North Wall Quay, Dublin 1, Ireland. **Pack Sizes & NHS price**: Sialanar 250 ml bottle £320. Sialanar 60ml Bottle £76.80. **Marketing Authorisation Numbers:** ***Great Britain:*** PLGB 42588/0003. ***Northern Ireland:*** Sialanar 250 ml bottle - EU/1/16/1135/001; Sialanar 60ml Bottle - EU/1/16/1135/002

Adverse events should be reported.

Reporting forms and information can be found at: www.mhra.gov.uk/yellowcard.

Adverse events should also be reported to Proveca Limited.

Phone: +44 333 200 1866
E-mail: medinfo@proveca.com

For the Republic of Ireland

Marketing Authorisation Holder: Proveca Pharma Ltd. 2 Dublin Landings, North Wall Quay, Dublin 1, Ireland. **Pack Sizes:** Sialanar 250 ml Bottle. Sialanar 60ml Bottle (hospital use only). **Marketing Authorisation Numbers:** Sialanar 250 ml bottle - EU/1/16/1135/001; Sialanar 60 ml Bottle - EU/1/16/1135/002

Adverse events should be reported.

Reporting forms and information can be found at: www.hpra.ie

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