CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

GLYCOPYRROLATE ORAL SOLUTION (CUVPOSA)

(Medexus Pharmaceuticals, Inc.)

Indication: Chronic severe drooling, neurologic (pediatric).

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Abbreviations

AE	adverse event
AUC	area under the curve
CDR	CADTH Common Drug Review
CI	confidence interval
CP	cerebral palsy
DB	double blind
DIS	Drooling Impact Scale
DSFS	Drooling Severity and Frequency Scale
ECSIO	Evaluation of Change and Satisfaction for Individualized Outcomes
GERD	gastroesophageal reflux disease
GI	gastrointestinal
HRQoL	health-related quality of life
LOCF	last observation carried forward
mITT	modified intention to treat
mTDS	modified Teacher's Drooling Scale
MCID	minimal clinically important difference
PP	per protocol
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
VAS	Visual Analogue Scale
WOCF	worst observation carried forward

Drug	Glycopyrrolate (Cuvposa)
Indication	To reduce chronic severe drooling in patients aged 3 to 18 years with neurologic conditions associated with problem drooling (e.g., cerebral palsy)
Reimbursement request	As per indication
Dosage form(s) and route of administration and strength(s)	Oral solution, 1 mg/5 mL
NOC date	October 30, 2017
Sponsor	Medexus Pharmaceuticals, Inc.

Executive Summary

Introduction

Children with neurologic disorders, such as cerebral palsy (CP), may have difficulty controlling their saliva. This is a condition that is well known to affect children with CP. Most individuals with CP produce normal amounts of saliva;[1] however, the estimated prevalence of excessive drooling (also known as sialorrhea), is between 10% and 58% among CP patients.[2] According to the Ontario Federation for Cerebral Palsy, it is estimated that approximately 60,000 patients with CP in Canada have sialorrhea.[3]

Sialorrhea is common in infants. However, by approximately two years of age, children with typical development should have the ability to perform most activities without loss of saliva.[4] After four years of age, sialorrhea may be recognized as abnormal and often persists in children with neurologic disorders, including neuromuscular incoordination of swallowing and intellectual disabilities.[2] Sialorrhea can have a significant medical and psychosocial impact, as drooling can be quite emotionally distressing for children with CP, as well as for their parents and caregivers.[5] It can cause constant damp, soiled clothing; unpleasant odour; irritated, chapped, or sore skin around the mouth and chin; skin and mouth infections; dehydration; mastication challenges; interference with speech; and damage to possessions. It also increases social isolation as it can be stigmatizing. In Canada, four treatment modalities exist for addressing the symptoms of excessive drooling: surgery, botulinum toxin injections, physical therapy, and drug therapy.[5]

Anticholinergic drugs are used to treat sialorrhea. These drugs inhibit parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine. They indirectly reduce the rate of salivation by preventing the stimulation of muscarinic receptors. Glycopyrrolate oral solution is one such anticholinergic drug. Unlike other anticholinergic drugs, glycopyrrolate does not easily cross the blood-brain barrier, which can make it more tolerable in patients with central nervous system impairment.

The objective of this report is to perform a systematic review of the beneficial and harmful effects of glycopyrrolate oral solution (1 mg/5 mL) indicated to reduce chronic severe drooling in patients three to 18 years of age with neurologic conditions associated with problem drooling.

Stakeholder Engagement

Patient Input

No patient input was received for this CADTH Common Drug Review (CDR).

Clinician Input

The following input is a summary of information provided by one clinical specialist with expertise in the diagnosis and management of chronic severe drooling in pediatric patients.

The most common treatment for sialorrhea in Canada is botulinum toxin injection. Glycopyrrolate oral solution is unlikely to change the treatment paradigm. There are a host of medical goals, but the social goal of drool reduction is preponderant — to facilitate socialization and improve family dynamics. One of the challenges in assessing the efficacy and utility of sialorrhea treatments is the absence of universally accepted and well validated outcome scales. Glycopyrrolate has a role in the therapeutic landscape, complementing the surgical and non-pharmaceutical options. It is best suited for patients whose neurologic conditions cause them to be intolerant of drugs that more easily cross the blood-brain barrier.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One phase III randomized controlled trial (RCT) was included in the systematic review. The pivotal study, FH-00-01 (N = 38), was a multi-centre, randomized, double-blind, placebo-controlled, eight-week study conducted at multiple sites in the US and was designed to assess the safety and efficacy of oral glycopyrrolate liquid (1 mg/5 mL) compared with placebo in the management of problem drooling in children with CP or other neurologic conditions. Patients enrolled in this study were between three and 16 years of age and exhibited severe drooling. They were randomized in a 1:1 ratio to either glycopyrrolate or placebo. The dose of glycopyrrolate was titrated during the first four weeks of the study. The primary outcome was the treatment responder rate based on the modified Teacher's Drooling Scale (mTDS) at week 8 (the change in mTDS score from baseline to week 8 was also reported). Secondary outcomes included the responders and change from baseline on the mTDS at weeks 2, 4, and 6, and patient or caregiver and physician global assessments.

Efficacy Results

Study FH-00-01 assessed the change in degree of drooling using the mTDS (Table 1). The primary outcome was the difference in responder rate based on the mTDS at week 8. A responder was defined as a patient whose mTDS score improved by at least three units in the observed time period. The responder rate at week 8 was statistically significantly higher for the glycopyrrolate (47%) than for the placebo (6%) group (P = 0.004). Further, statistically significantly more glycopyrrolate-treated patients were classified as responders at weeks 2, 4, and 6 compared with placebo-treated patients. In addition, mean improvements in change from baseline at week 8 were statistically significantly greater in the glycopyrrolate group than in the placebo group (–3.5 versus –0.1; P = 0.019). Although

a change of greater than or equal to three units on the mTDS is considered meaningful by the FDA, no minimal clinically important difference (MCID) for the mTDS was identified in the literature.

Health-related quality of life (HRQoL) was not measured in Study FH-00-01, however, treatment satisfaction was assessed at week 8 using caregiver and physician global assessment and was a secondary end point. Nineteen (100%) parents or caregivers of glycopyrrolate-treated patients, versus nine (56%) parents or caregivers of placebo-treated patients agreed that the treatment was "worthwhile" (P = 0.002). Similarly, 16 (84%) physicians in the glycopyrrolate group versus seven (41%) in placebo group agreed that the treatment was "worthwhile" (P = 0.014). However, none of the secondary outcomes in Study FH-00-01 were adjusted for multiplicity and no information pertaining to the MCID for the global assessment was identified in the literature.

Reduction in salivary production and reduction in unwanted symptoms were also identified as efficacy outcomes of interest in the CDR systematic review protocol, however, these outcomes were not assessed in the clinical trial included in this review.

Harms Results

In the pivotal Study FH-00-01, all 20 patients treated with glycopyrrolate experienced AEs, of which eight patients (40%) had mild AEs, seven (35%) had moderately severe AEs, and five (25%) had severe AEs. Sixteen patients (89%) in the placebo group experienced AEs, and all were mild or moderate in severity. The most common AEs were GI in nature: constipation, diarrhea, vomiting, and dry mouth.

In Study FH-00-01, one patient in the glycopyrrolate group experienced one serious adverse event (SAE) of generalized tonic-clonic seizure activity followed by generalized convulsions post-treatment.

In Study FH-00-01, two patients discontinued the study drug permanently because of AEs, one in each of the study groups.

No deaths were reported in Study FH-00-01.

This systematic review protocol had identified GI and respiratory AEs as being of particular interest. In terms of GI AEs in Study FH-00-01, the glycopyrrolate group had 17 (85%) patients with GI events, while the placebo group had nine patients (50%) with GI events. Of these, four (20%) patients in the glycopyrrolate group reported severe GI AEs compared with no patients in the placebo group. The most common GI complaints in the glycopyrrolate and placebo groups respectively were: constipation (seven [35%] versus three [17%]), diarrhea (three [15%] versus four [23%]), vomiting (eight [40%] versus two [11%]), and dry mouth (eight [40%] versus two [11%]).

Study FH-00-01 reported 14 (73%) respiratory AEs, with nine (45) in the glycopyrrolate group and five (28%) in the placebo group. Nasal congestion was the most common condition in this category, with six (30%) and two (11%) cases in the respective study groups.

Table 1: Summary of Key Results for Study FH-00-01

Outcome	FH-00-01		
	Glycopyrrolate (N = 19)	Placebo (N = 17)	P value
mTDS responder rate, n (%) per-protocol population			
Week 8	9 (47%)	1 (6%)	0.004
Week 6	10 (53%)	1 (6%)	0.002
Week 4	10 (53%)	2 (12%)	0.007
Week 2	7 (37%)	0 (0%)	0.005
Efficacy: Change from baseline in mTDS, per-protocol population			
Baseline, mean (SD)	7.0 (1.6)	5.8 (1.8)	NA
Mean improvement from baseline after 8 weeks (SD)	–3.5 (1.9)	–0.1 (1.8)	0.019
Harms			NA
Safety population	N = 20	N = 18	
Patients with > 0 AEs, n (%)	20 (100%)	16 (89%)	NA
Patients with > 0 SAEs, n (%)	1 (5%)	0 (0%)	NA
WDAEs, n (%)	1 (5%)	1	NA
Deaths	0	0	NA
Notable harms: safety population (n = 38)			
Dry mouth, n (%)	8 (40%)	2 (11%)	NA
Nasal congestion, n (%)	6 (30%)	2 (11%)	NA
Constipation, n (%)	7 (35%)	3 (17%)	NA
Vomiting, n (%)	8 (40%)	2 (11%)	NA

AE = adverse event; mTDS = modified Teacher's Drooling Scale; NA = not available; SAE = serious adverse events; SD = standard deviation; WDAE = withdrawal due to adverse events.

Sources: FH-00-01 Clinical Study Report.[6]

Critical Appraisal

In both study groups of Study FH-00-01, there was a high proportion of patients (> 80%) who completed the eight-week study period. However, 13 of these 18 (75%) patients in the glycopyrrolate group missed at least one dose of study drug compared with seven of the 15 (44%) completers in the placebo group. Therefore, there could be a bias leading to an underestimation of treatment effect in favour of glycopyrrolate.

The high incidence of AEs in Study FH-00-01 (e.g., constipation, vomiting, and dry mouth) in patients in the glycopyrrolate group, or lack of efficacy in patients who received placebo, could have sacrificed patient or caregiver blinding of treatment. This potential unblinding may have introduced bias in outcome measures, specifically in the subjective scales of drooling severity and frequency, such as mTDS, the Drooling Impact Scale (DIS), and the Drooling Frequency and Severity Scale (DSFS). Further, in Study FH-00-01, four patients had previously taken antidrooling drugs. Two patients (10%) in the glycopyrrolate group had tried scopolamine patches and two (11%) in the placebo group had tried Robinul (another glycopyrrolate formulation). This experience with other anticholinergic medications may have affected blinding as patients and caregivers would have already been familiar with the expected drooling outcomes and AEs.

Nevertheless, in Study FH-00-01, the magnitude of difference between treatment groups in terms of the percentage decrease in the scores was recognized as both statistically and clinically significant given the relatively small sample size. The per-protocol analysis results were generally consistent with modified intention-to-treat (mITT) analysis results. It is unlikely that such a substantial difference could be attributable to random effect or any other factors except for the treatment.

No Canadian patients were included in Study FH-00-01. Patients in the trial met clinical criteria for severe drooling. The study included patients with intellectual disability and those reliant on feeding tubes and excluded pregnant females. Therefore, the patient population was broadly reflective of the relevant clinical populations for this drug. The dose and administration of glycopyrrolate was appropriate and relevant. Study FH-00-01 employed the four-week titration procedure recommended by the sponsor for establishing the appropriate dose, and dose strength was within the range specified in the Product Monograph.

No comparative evidence for glycopyrrolate was identified and no indirect evidence was submitted by the sponsor. An independent literature search for indirect evidence conducted by CADTH did not identify any evidence that met the inclusion criteria of the CDR review protocol. Therefore, the benefit of glycopyrrolate compared with other treatments for severe drooling used in Canadian clinical practice is unknown.

Study FH-00-01 was of relatively short duration given that treatment with glycopyrrolate is anticipated to be used on a chronic basis. Study FH-00-01 was eight weeks in duration, and while this duration may be adequate to detect a response to treatment, the long-term benefit of glycopyrrolate remains uncertain.

Other Relevant Evidence

Study Sc-GLYCO-06-01 was a 24-week, multi-centre, open-label study designed to assess the long-term efficacy and safety of oral glycopyrrolate liquid (1 mg/5 mL) for the treatment of chronic, moderate to severe drooling in pediatric patients with CP or other neurologic conditions. Patients enrolled in Study Sc-GLYCO-06-01 could be naive or non-naive with respect to prior treatment with oral glycopyrrolate liquid. The baseline characteristics of patients in the Sc-GLYCO-06-01 study were generally similar to patients in the FH-00-01 study. Key limitations of Study Sc-GLYCO-06-01 were related to the open-label, single-arm design of the study.

Results of Study Sc-GLYCO-06-01 may suggest improvement in drooling based on the mTDS after 24 weeks of treatment with glycopyrrolate liquid. Responders were defined as those showing at least a three unit improvement in mTDS. The percentage of patients classified as responders at week 24 were: 48.1% (95% confidence interval [CI], 36.9 to 59.2) in the naive group and 51.9% (95% CI, 36.9 to 59.2) in the non-naive group. At the end of the study, 85.7% of parents or caregivers in the naive group, and 80.4% of parents or caregivers in the non-naive group agreed or strongly agreed with the statement: “This is a worthwhile treatment.” Overall, efficacy results were aligned with those of Study FH-00-01.

In terms of harms, 90.5% of patients in the naive group and 86.8% of patients in the non-naive group experienced an AE. The most common AEs were attributed to constipation (20.4%), vomiting (17.5%), and diarrhea (17.5%). Overall, the incidence of AEs appeared to increase as the dose of glycopyrrolate increased. Fewer AEs related to GI and respiratory events were observed in the 24-week Sc-GLYCO-06-01 study compared with the eight-week pivotal trial (FH-00-01), but the higher number of GI AEs in Study FH-00-01 may be artificially inflated due to the small sample size of this study. No new safety signals arose over the course of the 24-week Sc-GLYCO-06-01 study compared to the eight-week pivotal trial (FH-00-01).

Conclusions

One phase III RCT comparing glycopyrrolate to placebo (FH-00-01) was included in the CDR systematic review of glycopyrrolate oral solution to reduce chronic drooling. Study FH-00-01 demonstrated that in children with neurologic impairments (e.g., CP), orally administered glycopyrrolate is an effective agent for reducing excessive drooling. The responder rate on the mTDS at week 8 was statistically significantly higher in patients treated with glycopyrrolate than placebo. Study FH-00-01 was associated with methodological limitations, including subjective, non-validated outcome measures to assess the change in degree of drooling, and potential for unblinding.

A high proportion of patients treated with glycopyrrolate experienced similar GI AEs, such as constipation and vomiting, and dry mouth. SAEs occurred infrequently in Study FH-00-01. No new safety signals arose over the course of the 24-week Sc-GLYCO-06-01 study compared to the eight-week pivotal trial (FH-00-01).

There is no direct or indirect evidence comparing the efficacy or safety of glycopyrrolate oral solution to other treatments used in Canadian clinical practice for severe drooling (atropine, benztropine, botulinum toxin, trihexyphenidyl, or surgical interventions) in children with neurologic conditions.

Introduction

Disease Background

Sialorrhea (drooling or excessive salivation) is a common problem in neurologically impaired children and in adults who have injuries or insults, such as Parkinson disease or stroke. It is most commonly caused by poor oral and facial muscle control. Contributing factors may include hypersecretion of saliva, dental malocclusion, postural problems, and an inability to recognize salivary spill.[7] No clear clinical criteria exist to describe hypersalivation or pathologic saliva production.[8]

Sialorrhea is common in infants. However, at 24 months of age children with typical development should have the ability to perform most activities without loss of saliva.[2] After the age of 4 years, sialorrhea is unusual and often persists in children with neurologic disorders, including neuromuscular incoordination of swallowing and intellectual disabilities.[2] It is a condition well known to affect children with CP and other neurologic disabilities. While most individuals with CP produce normal amounts of saliva,[6] excessive drooling occurs in approximately 40% of this pediatric population,[9] though the prevalence rate ranges from 10% to 58% of patients with CP.[2] This presentation can have a significant medical and psychosocial impact, as drooling can be quite distressing for children with CP, as well as for their parents and caregivers.[5]

Predisposing factors of sialorrhea in children with CP include having the non-spastic type of CP, having the quadriplegic topographical pattern, the absence of cervical control, severe difficulties in gross motor coordination or function, epilepsy, intellectual disability, lack of speech, open anterior bite, and dysphagia.[9] Currently, it is widely accepted that sialorrhea in children with CP is not caused by hypersalivation, but by oral motor dysfunction, dysphagia, and/or intraoral sensitivity disorder.[1]

There is a positive correlation between sialorrhea in children with CP and difficulties in the formation of the food bolus, inefficient labial sealing, suction disorder, increased food residue, difficulty controlling the lips, tongue, and mandible, reduced intraoral sensitivity, reduced frequency of spontaneous swallowing, esophageal phase dysphagia, and dental malocclusion.[10] Saliva plays an important role in protecting the esophageal mucosa against lesions caused by gastroesophageal reflux disease (GERD). In children with sialorrhea, the constant loss of saliva can hinder the removal of gastric acid reflux in the esophagus, which can perpetuate esophageal dysmotility and esophagitis.[10]

Sialorrhea can be classified as “anterior” and “posterior”; both can occur separately or simultaneously. Posterior drooling occurs in patients with severe oropharyngeal dysphagia. Posterior sialorrhea is the flowing of saliva from the tongue to the pharynx.[11] Posterior pooling can have the serious consequence of chronic aspiration resulting in recurrent infections and progressive lung disease. In contrast, anterior sialorrhea is the unintentional loss of saliva from the mouth. While posterior drooling has serious medical implications, anterior drooling is the more noticeable of the two types, as it features saliva dripping from the mouth.

Anterior drooling can result in the need for frequent clothing changes, may damage possessions such as books, computers, and toys, and may spray from the mouth while talking. The presence of saliva on the chin can lead to frequent wiping, causing skin irritation and breakdown. Unpleasant odours, mouth infections, dehydration, impaired mastication, and

speech impairment can also result.[5] Social embarrassment experienced by children with excessive drooling, their caretakers, and siblings can be considerable and may lead to isolation and low self-esteem. Children with CP who drool are often subsequently stigmatized and are misperceived as having intellectual deficiencies. The morbidity of sialorrhea extends beyond its physical effects into the broader web of psychosocial wellbeing, for both the affected children and parents.[2,5] Indeed, drooling is one factor impeding socialization, interpersonal relationships, and integration into society for individuals with disabilities.[1]

Standards of Therapy

Numerous therapies, both medical and surgical, are currently available for the treatment of sialorrhea, but none have been associated with optimal results. Management includes feeding programs to increase frequency of swallowing and oral stimulation, behavioural modification programs, medications, and/or surgery. In severe cases, patients require frequent suctioning and pulmonary hygiene, neither of which may sufficiently maintain normal function. The investment of time and resources that such treatment necessitates is considerable.[10] The following is a summary of the four major domains of therapy: physical therapy, surgery, botulinum toxin, and pharmacotherapy.

Physical Therapy

Physical therapy involves the correction of general body posture and head posture to eliminate the anterior loss of saliva from the oral cavity. Therapy can also seek to improve lip and jaw closure as well as increase tongue control.[12] There are no reported adverse effects associated with physical therapy. Approaches include exercises for orofacial muscles, speech therapy, auditory feedback training for improved muscle control, and tongue positioning.[12]

Related to physical therapy are rare, technologically mediated approaches, including proprioceptive neuromuscular facilitation to restore and retrain muscle function, neuromuscular electrical stimulation to increase facial muscle movements, and radiotherapy in excess of 600 rads, which introduces the risk of sarcomas and dental caries.[12]

Botulinum Toxin

Botulinum toxin A is the most common neurotoxin used to treat drooling. It inhibits the release of acetylcholine at the neuroglandular junction, reducing the amount of saliva produced by the salivary glands.[5] AEs can relate to trauma at the injection site as well as be associated with the botulinum toxin itself.[1] These AEs include pain, hematoma, intraoral blood, swallowing difficulty associated with swelling of the salivary gland, infection, and possible trauma to the facial nerve when injecting the parotid gland.[1] AEs associated with the botulinum toxin itself include excessively dry mouth, problems with mastication, facial weakness, recurrent mandibular dislocation, and fever.[13]

Botulinum toxin as a treatment for drooling varies widely across a number of factors, including the product name, the clinician performing the injection, the dosing, the needle caliber, and the number of injection sites. As a result, the safe maximum dose and ideal application method have not been established.[5]

Other Pharmacotherapies

Drug interventions work by decreasing the volume of saliva produced in the oral cavity and in the GI tract. The salivary glands are controlled by the parasympathetic autonomic nervous system. Thus, anticholinergic drugs that reduce salivary flow are the most frequently used type of drug.[10] The anticholinergic drugs most commonly used are atropine, benztropine, glycopyrrolate bromide, benzhexol hydrochloride (also known as trihexyphenidyl), and scopolamine.[5] Drugs vary in their method of delivery, dosing, frequency of delivery, and length of treatment. They can be administered orally, intravenously, topically as dermal patches, intramuscularly, and via nebulization.[14]

None of these pharmacotherapies are approved for the treatment of drooling in a pediatric population in Canada, though trihexyphenidyl (available as a tablet or oral solution) and benztropine (available as a tablet, injection, or oral solution) are approved for treating symptoms associated with parkinsonism. Atropine, given by injection, tablet, or oral solution, is used for the treatment of poisoning by susceptible organophosphorous nerve agents having anticholinesterase activity. Scopolamine (also known as hyoscine) is available as an injection, oral solution, or skin patch and is most commonly indicated for treating motion sickness.

Side effects from medications include xerostomia, thick mucoid secretions, dehydration, urinary retention, urinary tract infections, constipation, facial flushing, skin rash, fever, dizziness, drowsiness, headache, dilated pupils, blurred vision, epilepsy, and GERD.[15,16]

Off-label use of glycopyrrolate tablets has been shown to decrease drooling in children. These tablets require compounding to treat pediatric patients, resulting in highly variable pharmacokinetics and widely ranging effective dosages.[17]

Surgery

Surgical management aims at the reduction of saliva production.[18] It can quickly lead to an effective reduction in sialorrhea, but with side effects, including the possible exacerbation of GERD and esophagitis.[18] Surgical treatment for sialorrhea can include parotid ductal relocation or the removal of submandibular glands. Radical procedures, such as bilateral division of the parotid ducts with removal of the submandibular glands and neurectomies, have been proposed, but with unpredictable results.[10] Facial nerve paralysis, excessive dryness of the mouth, dental decay, and hypertrophic facial scars have all been reported as post-operative complications.[10] Surgical procedures are described as follows:

- Denervation works by eliminating parasympathetic stimulation to the salivary glands. It can result in hearing loss and permanent taste loss, as well as an increase in thick mucoid saliva. Its advantage is that there are no external excisions to the face.[19]
- Submandibular gland rerouting involves transferring the submandibular ducts behind the tongue base, directing salivary flow posteriorly. It is contraindicated in children with a history of aspiration pneumonia. Its side effects include post-operative pain and ranula formation.[20]
- Submandibular gland ligation entails surgically tying the salivary gland ducts. The procedure increases the risk of developing submandibular salivary gland stones due to saliva retention.[21]

- Submandibular gland excision involves the removal of the submandibular gland(s) transorally, transcervically, or endoscopically.[5] Side effects include xerostomia (dry mouth) with resulting negative impact on mastication and dental health, external scarring, and risk of nerve damage.[22]
- Sublingual gland excision involves the removal of the sublingual gland. It involves extensive floor of mouth resection and side effects include potentially longer hospital stay, lingual nerve palsy, and a heightened risk of post-operative hemorrhage.[23]
- Parotid duct rerouting redirects salivary flow and requires general anesthetic. Side effects include the risk of sialocele and increase in aspiration.[24] Transoral parotid duct ligation, on the other hand, involves minimal surgical resection and low morbidity.[25] Parotid duct rerouting is associated with a risk of infection and ranula.[5]

Drug

Glycopyrrolate for injection has been approved in Canada since 2005 for GI conditions and for anesthetic purposes. Inhaled glycopyrronium bromide has been approved since 2014 for chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. Glycopyrrolate oral tablets — Robinul and Robinul Forte Tablets — were first approved in 1993 and 2002, respectively, but were cancelled post market in 2010. There are currently no orally administered glycopyrrolate products marketed in Canada.

Glycopyrrolate is a synthetic quaternary ammonium anticholinergic agent that does not easily cross the blood-brain barrier. Glycopyrrolate inhibits the action of acetylcholine on salivary glands, thereby reducing the extent of salivation. It is a competitive inhibitor of acetylcholine muscarinic receptors that are located on salivary glands. Glycopyrrolate indirectly reduces the rate of salivation by preventing the stimulation of these receptors.[26,27]

Glycopyrrolate oral solution (referred to as glycopyrrolate hereafter) is approved in Canada to reduce chronic severe drooling in patients three to 18 years of age with neurologic conditions associated with problem drooling (e.g., CP).[26] Glycopyrrolate is available as a 1 mg/5 mL clear, cherry-flavoured solution for oral administration. Each mL of oral solution contains 0.2 mg of glycopyrrolate.[26] Dosing of glycopyrrolate oral solution is based on body weight and should be taken within two hours after meals. Dosing should be initiated at 0.02 mg/kg orally three times daily and titrated in increments of 0.02 mg/kg every 5 to 7 days based on therapeutic response and adverse reactions. The maximum recommended dosage is 0.1 mg/kg three times daily, not to exceed 1.5 to 3 mg per dose based upon weight.[26] Once an initial dose has been selected, clinical signs can be used to titrate the dose of oral glycopyrrolate solution for each child over several weeks until control of drooling is satisfactory, with maintenance dose individualized for each child.[17]

Table 2: Key Characteristics of Glycopyrrolate

	Glycopyrrolate
Mechanism of action	Anticholinergic inhibition of salivary glands
Indication	To reduce chronic severe drooling in patients 3 to 18 years of age with neurologic conditions associated with problem drooling (e.g., cerebral palsy)
Route of administration	Oral
Recommended dose	Initiate dosing at 0.02 mg/kg orally three times daily and titrate in increments of 0.02 mg/kg every 5 to 7 days based on therapeutic response and adverse reactions. The maximum recommended dosage is 0.1 mg/kg three times daily not to exceed 1.5 to 3 mg per dose based upon weight.
Serious adverse effects or safety issues	The most common AEs are dry mouth, constipation, and flushing. AEs leading to discontinuation most commonly involved the gastrointestinal system organ class (vomiting and constipation) and psychiatric disorders (abnormal behaviour).
Other	It is also not known whether glycopyrrolate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. It is not known whether this drug is excreted in human milk. It is not indicated in children less than 3 years of age or adults older than 65 years.

AE = adverse effect.

Source: Product Monograph for Cuvposa.[26]

Stakeholder Engagement

Patient Group Input

No patient input was received for this CDR review.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by one clinical specialist with expertise in the diagnosis and management of sialorrhea.

Description of the Current Treatment Paradigm for the Disease

Sialorrhea can be classified as either primary (increased saliva production) or secondary (spillage of saliva from the oral cavity secondary to oromotor dysfunction, decreased swallowing, or cognitive impairment). Treatment of primary sialorrhea is targeted to the cause of the increased saliva production. However, primary sialorrhea is far less common than secondary sialorrhea. The aim of treatments for secondary sialorrhea is to either increase awareness, improve swallowing function and frequency, or simply to decrease the amount of saliva produced. Treatments can be classified as non-surgical, minimally invasive, or invasive treatments.

Non-surgical therapies include oromotor therapy (working on speech and swallowing with a therapist), strategies to increase awareness and swallowing frequency (e.g., reminders to swallow, mirrors, wrist bands, water bottle, chewing gum), and behavioural therapy to curtail behaviours, such as oral stimulation and purposeful soiling of the environment for attention seeking. Finally, pharmacotherapy is employed using agents with anticholinergic properties.

The most common minimally invasive treatment is direct injection of botulinum toxin into the major salivary glands (parotid and submandibular glands). This treatment is the most commonly employed treatment across Canada.

The invasive treatments involve surgery. The most common surgical treatments are ligation of the ducts of the major salivary glands, rerouting of the submandibular ducts, and gland excision.

It is important to note that botulinum toxin treatments and surgery for secondary sialorrhea do not change the underlying disease mechanism. Rather they simply aim to decrease the amount of saliva produced which hopefully translates into less saliva spillage from the oral cavity.

Treatment Goals

The goals of treatment can be broadly classified as either medical or social. Medical goals include management of skin maceration, odour, dehydration, speech impairment, and risk of aspiration. Repeated aspiration may result in loss of lung function. The social goals

include improved family dynamics and caregiver fatigue, facilitation of schooling, and socialization.

Unmet Needs

The treatment gaps include non-responsiveness to treatment for some patients and lack of resolution of the underlying cause of secondary sialorrhea. Further, some patients may have difficulty accessing treatments as there are a lack of specialized care centres focusing on sialorrhea, and not all patients have access to specialized care centres due to geographical or medical conditions that render travel to specialized centres problematic.

Place in Therapy

This drug offers a mechanism of action that would complement other available treatments. The anticholinergic effect of the medication would augment the effect of botulinum toxin and surgical intervention. When combined with botulinum toxin, there is a risk that the saliva produced becomes very thick and difficult to clear the throat causing airway issues (called a “mucus plug”).

Glycopyrrolate would decrease the symptoms of sialorrhea but would not change the underlying cause of secondary sialorrhea.

The clinical expert consulted by CADTH anticipates that the drug would not be used as a first-line treatment due to the possibility of other anticholinergic side effects. Rather, it is expected that the drug would likely be used in combination with other treatments or in non-responders to more common treatments. Therefore, the drug is not expected to cause a shift in the current treatment paradigm.

For secondary sialorrhea, botulinum toxin remains an effective option with limited risk of systemic effects and should be used as first-line treatment, where appropriate.

Patient Population

The clinical expert consulted by CADTH thought that most patients with secondary sialorrhea would benefit from this treatment. Ideal patients for this treatment may include: those that have failed other forms of established treatment; patients with severe sialorrhea requiring multiple modality treatment; patients that have had adverse reactions to botulinum toxin; patients that have difficulty accessing centres that provide treatment with botulinum toxin; and patients that are not candidates for surgical intervention or repeated anesthetics due to medical fragility.

Patients best suited for treatment would be identified primarily by clinician examination or judgment. The presentation is typically anterior sialorrhea. However, in instances of suspected recurrent aspiration, a swallow assessment or chest X-ray may be needed.

There are no issues related to diagnosis. The condition is easily recognized by caregivers and clinicians.

Pre-symptomatic patients should not be treated with glycopyrrolate. Others who should not receive glycopyrrolate treatment include patients with a history of adverse reactions to anticholinergic medications, patients susceptible to other anticholinergic effects (e.g., urinary retention, constipation, ophthalmologic conditions), patients with poor swallowing and an inability to clear the thick secretions that may develop with anticholinergic treatment,

or patients with medical conditions requiring treatment with medication that interacts with anticholinergic treatment.

Assessing Response to Treatment

There are several outcome measures used. Most are subjective and based on the amount of saliva spillage from the oral cavity. The most relevant outcome measures should be derived from the caregiver goals of treatment. A clear improvement of the stated goals should be used to determine whether a patient is responding to treatment. Current outcome measures include the weighing of bibs; drooling quotient (i.e., a count of each drooling episode); collection of absorbent cotton dental rolls from the oral cavity; subjective measures (e.g., DIS); and Evaluation of Change and Satisfaction for Individualized Outcomes (ECSIO), which is a combination of patient- and family-centred goals with an overall quality of life measurement using a Visual Analogue Scale (VAS).

Clinically meaningful outcomes include a reduction in the frequency and severity of the sialorrhea; reduction in the frequency of required clothing changes; health improvement (e.g., less frequency of aspiration, skin improvement); and enhanced socialization.

Treatment response should be assessed at every health visit. As stated above, in addition to assessing response, undesired systemic anticholinergic effects should also be assessed, however, there is a lack of a reliable outcome measures to measure treatment success.

Discontinuing Treatment

Treatment should be discontinued if there is no response to treatment, severe systemic anticholinergic effects, or an allergic reaction to the drug therapy.

Prescribing Conditions

Treatment should be initiated by a specialist in a field such as pediatrics, complex care, neurology, or otolaryngology. Ongoing monitoring can be undertaken by primary care physicians. Treatment could be administered in the community, hospital (inpatient and outpatient setting), and in specialty clinics (complex care or saliva management clinics).

Clinical Evidence

The clinical evidence included in the review of glycopyrrolate is presented in three sections. The first section is the systematic review, which includes pivotal studies provided in the sponsor's submission to CDR and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section is intended to include indirect evidence from the sponsor (if submitted) and indirect evidence selected from the literature that met the selection criteria specified in the review. However, no indirect evidence was submitted by the sponsor nor was any indirect evidence that met the selection criteria specified in the review identified from the literature. The third section includes one sponsor-submitted, long-term extension study.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of glycopyrrolate oral solution (1 mg/5 mL) indicated to reduce chronic severe drooling in patients three to 18 years of age with neurologic conditions associated with problem drooling (e.g., CP).

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CDR and Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient population	Children 3 to 18 years of age with neurologic conditions and problem drooling **Subgroups:** Underlying neurologic condition (e.g., cerebral palsy) Severity of underlying condition	
Intervention	Glycopyrrolate (oral solution, administered 0.02 to 0.1 mg/kg three times a day)	
Comparators	• Atropine • Benztropine • Botulinum toxin	• Scopolamine (hyoscine) • Trihexyphenidyl • Surgical interventions
Outcomes	**Efficacy outcomes:** • Change in degree of drooling (severity and frequency; measured by the mTDS and VAS) • Health-related quality of life • Reduction in salivary production (e.g., swab method) • Reduction in unwanted symptoms (e.g., skin chafing, *Candida albicans*, odour) **Harms outcomes:** AEs, SAEs, WDAEs, mortality, gastrointestinal AEs (constipation, perforated bowel), respiratory AEs	
Study design	Published and unpublished phase III and IV RCTs	

AE = adverse event; mTDS = modified Teacher's Drooling Score, RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse events; VAS = Visual Analogue Scale.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS (Peer Review of Electronic Search Strategies) checklist (https://www.cadth.ca/resources/finding-evidence/press).[28]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Cuvposa (glycopyrrolate) and drooling. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Search Portal (ICTRP).

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on July 8, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on November 20, 2019.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist (https://www.cadth.ca/grey-matters).[29]:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug And Device Regulatory Approvals
- Advisories And Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (Free).

Google was used to search for additional internet-based materials. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 2 for more information on the grey literature search strategy.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

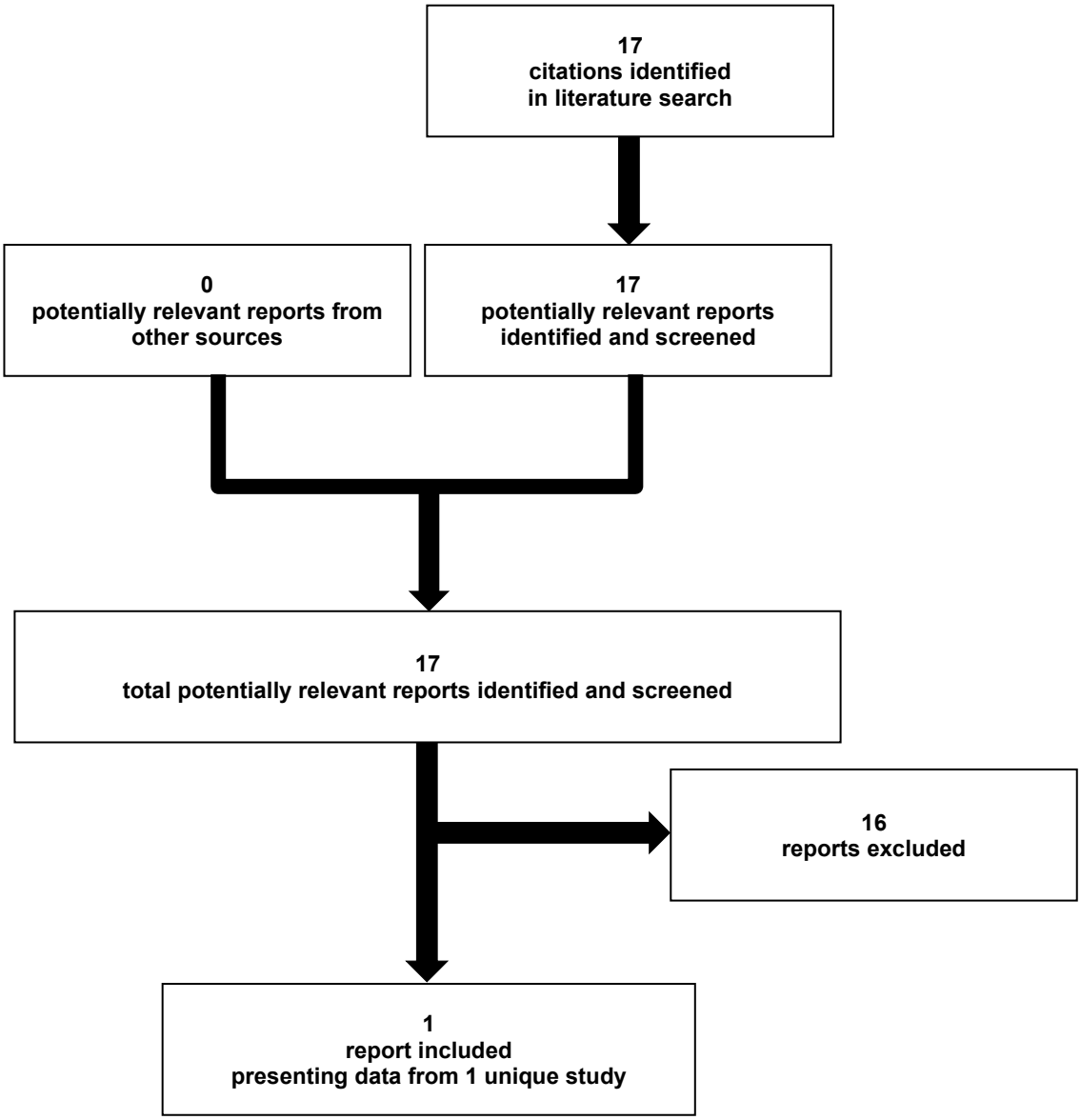


Table 4: Details of Included Studies

		FH-00-01
Designs and Populations	**Study design**	Multi-centre, double-blind, placebo-controlled RCT
	Locations	US
	Randomized (N)	38
	Inclusion criteria	• Weight at least 13 kg • Age 3 to 16 years • Previously diagnosed with cerebral palsy, intellectual disability, or another neurologic condition • Profuse, severe drooling in the absence of treatment so that clothing became damp on most days (approximately five to seven days per week).[a]
	Exclusion criteria	• Extent of drooling was wetness of the lips and chin, but clothes did not become damp on most days • Use of glycopyrrolate liquid within approximately 24 hours of baseline • Use of anticholinergic or cholinergic medications within three plasma half-lives of that medication prior to baseline • Injection with intrasalivary gland botulinum toxin within 10 months prior to baseline • Had undergone irradiation of salivary glands to reduce drooling • Had previous surgery to control sialorrhea • Had poorly controlled seizures defined as daily seizures • Had symptomatic gastroesophageal reflux (i.e., active vomiting) • Had known delayed gastric emptying • Had a history of intestinal obstruction • Medical conditions contraindicating anticholinergic therapy or treatment with glycopyrrolate
Drugs	**Intervention**	Glycopyrrolate oral solution 1 mg/5 mL 0.02 to 0.1 mg/kg three times a day; initial dose was 0.02 mg/kg three times a day and was titrated over a 4-week period to optimal response, with a maximum dose of 0.1 mg/kg or 3 mg, three times a day, whichever was less
	Comparator(s)	Matching placebo oral solution three times a day
Duration	**Phase**	
	Run-in	8 days
	Treatment phase	8 weeks (including a 4-week dose titration phase)
	Follow-up	None reported
Outcomes	**Primary end point**	• Responder rate: percentage showing ≥ 3 point change on the mTDS at week 8 • Change in mTDS from baseline to week 8
	Secondary and exploratory end points	• Daily mean parent/caregiver mTDS scores at weeks 2, 4, and 6 • AUC analysis of all mTDS evaluations from screening to week 8 • Proportion of patients who discontinued treatment due to lack of efficacy • Global assessments by the parent/caregiver, patients, and physicians at week 3
Notes	**Publications**	Zeller et al. (2012)[30]

AUC = Area Under the Curve; mTDS = modified Teacher's Drooling Scale; RCT = randomized controlled trial.

[a] If, in the absence of treatment, clothing, including bibs, shirts, or other clothing such as headbands used to catch drooling, was changed during the day because of dampness due to drooling, this was considered profuse, severe drooling for that day.

Source: FH-00-01 Clinical Study Report.[6]

Description of Studies

Study FH-00-01 was a multi-centre, US-based, randomized, double-blind, placebo-controlled, eight-week study designed to assess the safety and efficacy of oral glycopyrrolate liquid (1 mg/5 mL) compared with placebo in the management of drooling associated with CP or other neurologic conditions in 36 children (three to 16 years of age). Patients were randomized in a 1:1 ratio to either the glycopyrrolate (n = 20) or placebo group (n = 18). Randomization was done by stratified blocks with patients randomized in blocks of two. The study was conducted in various sites in the US from November 2002 to April 2007.

Those patients taking medications with anticholinergic or cholinergic activity underwent a washout phase prior to baseline, beginning eight days before randomization. After a four-week titration period to determine dosage to an optimal response, patients continued their optimal dose for the duration of the study. Two protocol amendments were made after the study had begun resulting in alterations to the inclusion criteria and to the primary efficacy end point. Originally, patients up to 18 years were age were eligible for study enrolment, however, the upper age limit was reduced to 16, requiring the replacement of two patients (one in each group) who had already been randomized. In addition, the original protocol called for efficacy to be determined by the mean change in mTDS from baseline. However, on a request from the FDA the primary end point was changed to the percentage showing a three point or greater change on the mTDS.

Populations

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria are listed in Table 4. Study FH-00-01 enrolled children 3 to 16 years of age with a minimal weight of 13 kg, a diagnosis of CP, intellectual disability, or similar neurologic condition, and with profuse, severe drooling characterized by damp clothing on most days. Of note, in Study FH-00-01, patients were excluded if they were previously treated with botulinum toxin within 10 months prior to the beginning of the trial, irradiation of salivary glands, or surgery to control drooling.

Baseline Characteristics

An overview of baseline characteristics for Study FH-00-01 is presented in Table 5. Most patients in both studies were male. The mean age of the patients in Study FH-00-01 was 10.8 and 9.3 years in each the glycopyrrolate and placebo groups, respectively. While most patients in the study had a diagnosis of CP (73%), patients with other neurologic conditions were also enrolled, including those with epilepsy and Rett syndrome. Drooling severity was comparable between treatment groups at baseline. In FH-00-01, three patients in each of the study groups had a previous treatment history with glycopyrrolate.

Table 5: Summary of Baseline Characteristics in Study FH-00-01 (Safety Population)

	Glycopyrrolate (N = 20)	Placebo (N = 18)
Age, years		
Mean (SD)	10.8 (4.7)	9.3 (4.7)
Range	4 to 23	3 to 20
Sex, n (%)		
Male	13 (65%)	9 (50%)
Female	7 (35%)	9 (50%)
Race/ethnicity, n (%)		
Caucasian	14 (70%)	5 (28%)
African-American	2 (10%)	7 (39%)
Asian	1 (5%)	0
Hispanic	3 (15%)	6 (33%)
Intellectual disability, n (%)	20 (100%)	18 (100%)
Underlying neurologic condition, n (%)		
Cerebral palsy	9 (75%)	7 (70%)
Epilepsy, ataxia, developmental delay, expressive aphasia non-ambulatory	0 (0%)	1 (10%)
Motor incoordination intellectual disability, non-verbal	0 (0%)	1 (10%)
Pervasive developmental disability	1 (8%)	0 (0%)
Rett syndrome	2 (17%)	0 (0%)
Seizures, static encephalopathy	0 (0%)	1 (10%)
Speech impairment, n (%)	20 (100%)	18 (100%)
Oral feeding problems, n (%)		
Present	10 (50%)	8 (44%)
Absent	10 (50%)	10 (56%)
Uses feeding tube, n (%)		
Yes	7 (35%)	5 (28%)
No	13 (65%)	13 (72%)
Patient residence, n (%)		
With parent	17 (85%)	17 (94%)
With foster parent	3 (15%)	1 (6%)
Nutritional status, n (%)		
Well-nourished	19 (95%)	16 (89%)
Under-nourished	1 (5%)	2 (11%)
Prior medications taken for drooling		
Robinul, n (%)	0 (0%)	2 (11%)
Scopolamine patches, n (%)	2 (10%)	0 (0%)
History of glycopyrrolate use, n (%)		
Yes	3 (15%)	3 (17%)
No	17 (85%)	15 (83%)

SD = standard deviation.

Note: Two patients were enrolled in the study before a protocol amendment restricted the upper age limit to 16 years of age. Consequently, these patients were removed from the per-protocol population and replaced. The two removed patients were included in the safety analyses.

Source: FH-00-01 Clinical Study Report.[6]

Interventions

In Study FH-00-01, doses of glycopyrrolate were titrated over a four-week period to optimal response, with the double-blind treatment period lasting eight weeks. Five dose levels of glycopyrrolate were employed: 0.02 mg/kg three times daily, 0.04 mg/kg three times daily, 0.06 mg/kg three times daily, 0.08 mg/kg three times daily, and 0.1 mg/kg three times daily (Table 6). Patients randomized to the glycopyrrolate group started at dose level 1, with a dose titration to the next level occurring every five to seven days until the optimal level was reached. No patient received more than 3 mg three times daily or dose level 5, whichever was less for the patient's weight category. Optimization was based on tolerance of side effects.

The drug was administered by a parent or caregiver at a place of their choosing, after training at the clinical site location. Parents and caregivers were instructed to administer the drug at least one hour before meals, when feasible. Patients with gastrostomy tubes received the drug via their feeding tubes.

Patients in the placebo group received a clear liquid placebo to match that was indistinguishable from the test drug and experienced the same titration schedule as those in the glycopyrrolate group.

Concomitant medications were used by 18 patients (90%) in the glycopyrrolate group and 100% of patients in the placebo group. The most frequently used concomitant medications were the muscle relaxant baclofen, used by nine patients (45%) in the glycopyrrolate group and five (28%) in the placebo group, and the stool softener polyethylene glycol, which was used by six patients (30%) in the glycopyrrolate group and six (33%) in the placebo group.

Other concomitant medications used by more than 10% of all study patients included: acetaminophen (10 patients [26%]); the antiepileptics levetiracetam (seven patients [18%]), oxcarbazepine (six patients, [16%]), carbamazepine (five patients, [13%]), and divalproex sodium (four patients, [11%]); the antiseizure medication Diastat (five patients, [13%]); the antibacterial (for systemic use) amoxicillin (five patients, [13%]); and ibuprofen for gynecological use (six patients, [16%]).

Table 6: Dose Titration Schedule From Study FH-00-01

Glycopyrrolate Liquid (1 mg/5 mL) Doses described were given three times daily.											
Weight		**Dose Level 1**		**Dose Level 2**		**Dose Level 3**		**Dose Level 4**		**Dose Level 5**	
Kg	**lb**	**(~0.02 mg/kg)**		**(~0.04 mg/kg)**		**(~0.06 mg/kg)**		**(~0.08 mg/kg)**		**(~0.1 mg/kg)**	
13-17	27-38	0.3 mg	1.5 mL	0.6 mg	3 mL	0.9 mg	4.5 mL	1.2 mg	6 mL	1.5 mg	7.5 mL
18-22	39-49	0.4 mg	2 mL	0.8 mg	4 mL	1.2 mg	6 mL	1.6 mg	8 mL	2.0 mg	10 mL
23-27	50-60	0.5 mg	2.5 mL	1.0 mg	5 mL	1.5 mg	7.5 mL	2.0 mg	10 mL	2.5 mg	12.5 mL
28-32	61-71	0.6 mg	3 mL	1.2 mg	6 mL	1.8 mg	9 mL	2.4 mg	12 mL	3.0 mg	15 mL
33-37	72-82	0.7 mg	3.5 mL	1.4 mg	7 mL	2.1 mg	10.5 mL	2.8 mg	14 mL	3.0 mg	15 mL
38-42	83-93	0.8 mg	4 mL	1.6 mg	8 mL	2.4 mg	12 mL	3.0 mg	15 mL	3.0 mg	15 mL
43-47	94-104	0.9 mg	4.5 mL	1.8 mg	9 mL	2.7 mg	13.5 mL	3.0 mg	15 mL	3.0 mg	15 mL
≥48	≥105	1.0 mg	5 mL	2.0 mg	10 mL	3.0 mg	15 mL	3.0 mg	15 mL	3.0 mg	15 mL

Source: FH-00-01 Clinical Study Report.[6]

Outcomes

A detailed description of outcome measures used in the trials included in this review is available in Appendix 3.

In Study FH-00-01, the primary efficacy end point was the responder rate, which was based on change in the mTDS as administered by the parent or caregivers, from baseline to week 8. A responder was defined as a patient whose mTDS score improved by at least three units in the observed time period. In the original protocol, the change in mTDS from baseline to week 8 was the primary outcome measure. However, this was changed at the request of the FDA to the percentage showing a three point or greater change on the mTDS. The mTDS assessments were conducted at baseline and on week 2, 4, 6, and 8.

Secondary efficacy end points were: repeat of the primary efficacy measure using daily mean parent or caregiver mTDS scores at weeks 2, 4, and 6; area under the curve (AUC) analysis of all mTDS evaluations from screening to week 8 using a two-sample Student t-test; analysis of the proportion of patients who dropped out of the study due to lack of efficacy in the glycopyrrolate liquid group versus placebo; and parent or caregiver's and physician's assessments at week 8.

The mTDS is 9-point subjective scale categorizing severity and frequency of drooling. The scale ranges from "1" (dry; never drools) to "9" (profuse frequent drooling, with clothing, hands, tray, and objects becoming wet). The mTDS is not a validated scale although it has been used in clinical studies for the assessment of drooling.[16,17,31] According to the sponsor's submission for glycopyrrolate, the use of the mTDS is specifically recommended by the US FDA Pediatric Advisory Subcommittee of the Antimicrobial Drugs Advisory Committee as an appropriate primary outcome variable for determining improvement in drooling.

Global assessments were conducted by physicians, caregivers, and patients with sufficient intellectual capacity. The Global Assessment is a 5-point scale (1 = strongly agree, 2 = agree, 3 = neutral, 4 = disagree, 5 = strongly disagree) applied to the statement, "This is a worthwhile treatment." Global assessment was conducted at week 8 or at study discontinuation.

No information pertaining to the MCID for the mTDS or global assessments was identified in the literature, though the FDA recognizes a three unit change in mTDS as being indicative of a treatment responder.

Statistical Analysis

In Study FH-00-01, a type I (alpha) error of 0.05 was applied to all statistical tests. Patients who dropped out had the lowest rank carried forward.

The primary outcome was the proportion of responders identified at week 8. Fisher exact test was employed to analyze the percent of responders. All randomized patients who received at least one dose of study drug and who were 16 years of age or older at the time of enrolment were included in the analyses of the primary efficacy end points. Analysis of the proportion of responders was done with an extended Cochran–Mantel–Haenszel test using modified ridit scores. In a supportive analysis to account for diurnal variation, each mTDS measurement at week 8 (i.e., morning, afternoon, and evening measures) was analyzed individually, and adjusted for the baseline mTDS scores at the same time point.

Assuming a primary efficacy end point of the mTDS where active-treated and placebo-treated patients showed changes from baseline to eight weeks of 2.4 units and 1.0 units, respectively, with a common standard deviation of change of 0.7 units, 10 patients per treatment arm were required for a statistical significance with 90% power and a type I (alpha) error of 0.05. A sample size of 10 patients per treatment group would yield 90% power with an alpha level of 0.05. Eighteen patients per treatment group were included, as approximately 30% of patients were expected to drop out of the study due to AEs or for other reasons. The final sample size of 38 patients suggests that this study was adequately powered.

None of the secondary outcomes were adjusted for multiplicity. A repeat of the primary efficacy measure used the daily mean parent/caregiver mTDS scores at weeks 2, 4, and 6. The AUC analysis of all mTDS evaluations from screening to week 8 used a two-sample t-test. The analysis of the proportion of patients who dropped out of the study due to lack of efficacy in the glycopyrrolate group was a secondary end point in the study, however, not statistical testing was conducted on this end point as only one patient discontinued for this reason. Global assessments at week 8 were analyzed using a binomial proportions test; for patients who discontinued prematurely, the last measure was carried forward to week 8.

Two patients enrolled and treated in the study were excluded from the per-protocol (PP) population because they were older than 16 years, and thus were in violation of the protocol amendment. All other patients were included in the analyses of efficacy data. In the event of early discontinuation, the patient was treated as a treatment failure in the analyses of the primary efficacy end point. The lowest rank carried forward was used to fill in missing values for the efficacy AUC calculations. No attempts were made to impute missing safety data.

Analysis Populations

The intention-to-treat (ITT) population consisted of all randomized patients. However, two patients were randomized to treatment before the protocol was amended to set an upper age limit of 16 years, and these patients no longer met the inclusion criteria. Consequently, these patients were included in the analysis of safety (n = 38) but excluded from the PP efficacy analyses (n = 36). Therefore, the primary analysis was conducted in the PP population, which consisted of all randomized patients who received at least one dose of study drug and who were 16 years of age or younger at the time of enrolment. The safety population consisted of all patients who received at least one dose of study drug.

Results

Patient Disposition

For the pivotal Study FH-00-01, 47 patients in total were screened for study participation. Of these, two patients withdrew consent, three withdrew for personal reasons, one had an AE during screening, two failed to meet inclusion criteria, and one was non-compliant. The remaining 38 patients were randomized into the study. A total of five patients withdrew from the study prematurely; two patients in the glycopyrrolate group and three patients in the placebo group.

Table 7: Patient Disposition

	FH-00-01	
	Glycopyrrolate	Placebo
Screened, N	47	
Randomized, N	20	18
Received treatment, N	19	17
Completed, N	19	17
Withdrawals AE Lack of efficacy Patient or parent decision	 1 0 1	 1 1 1
ITT, N	19	17
PP, N	19	17
Safety, N	20	18

AE = adverse event; ITT = intention to treat; PP = per protocol.

Source: FH-00-01 Clinical Study Report.[6]

Exposure to Study Treatments

Drug exposure data were not collected in the study's case report forms, so drug exposure was estimated based on records of missed and changed doses. Each patient could have received 168 doses throughout the eight-week study. Estimated mean glycopyrrolate exposure was 22.4 mL/day, with an estimated mean cumulative exposure of 1,336.0 mL over the entire eight-week study. Within the glycopyrrolate group, five (25%) missed no doses, while within the placebo group, eight of 18 patients (44%) in the safety population missed at least one dose.

In total, there were 57 up-titrations and 11 down-titrations for the 20 patients in the glycopyrrolate group, of whom 10 (50%) reached the maximum dose for weight. In the placebo group, there were 69 up-titrations and five down-titrations reported among the 18 patients, of whom 14 (78%) reached their maximum dose for weight.

Table 8: Study Drug Changes and Missed Doses: Safety Population

Characteristic	Glycopyrrolate (N = 20)	Placebo (N = 18)	Total (N = 38)
Number of patients with dose changes	20 (100%)	18 (100%)	38 (100%)
Number of patients with missed doses	15 (75%)	8 (44%)	23 (61%)
Number of patients with no missed doses	5 (25%)	10 (56%)	15 (39%)

Source: FH-00-01 Clinical Study Report.[6]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported below. See Appendix 3 for detailed efficacy data.

Change in Degree of Drooling

The primary outcome was the difference in responder rate based on the mTDS at week 8. The responder rate at week 8 was statistically significantly higher for the glycopyrrolate

(47%) than for the placebo (6%) group (P = 0.004; Table 9). As shown in Table 10, more glycopyrrolate-treated than placebo-treated patients were classified as responders at weeks 2, 4, and 6 compared with placebo-treated patients. By week 2, 7 (37%) patients in the glycopyrrolate group were responders compared with none in the placebo group. By week 4, both treatment groups achieved their maximum number of responders.

The original primary outcome measure, before the protocol change, was change from baseline in mTDS at week 8. As shown in Table 9, mean improvements in mTDS at week 8 were statistically significantly greater in the glycopyrrolate than in the placebo group (–3.5 versus –0.1; P = 0.019). The changes in mean mTDS from baseline for the glycopyrrolate and placebo groups respectively were: week 2: –2.3 (standard deviation [SD] = 3.0), 0.4 (SD = 1.2); week 4: –3.3 (SD = 1.9), –0.1 (SD = 2.1); week 6: –3.7 (SD = 1.9), –0.1 (SD = 1.9); and week 8: –3.5 (SD = 1.9), –0.1 (SD. = 1.8). The mean mTDS scores for each of weeks 2, 4, 6, 8, and baseline are shown in Figure 2.

Table 9: Summary of Primary Efficacy Results From Study FH-00-01 (PP Population)

Efficacy end point (week 8)	Glycopyrrolate (N = 19)	Placebo (N = 17)	Total (N = 36)	Statistical analysis
Responder rate				
Responder, n (%)	9 (47)	1 (6)	10 (28)	P = 0.004
Nonresponder, n (%)	9 (47)	16 (94)	25 (69)	
Change in mTDS from baseline to week 8				
n	16	14	30	Cochran–Mantel–Haenszel, P = 0.019
Baseline, mean (SD)	7.0 (1.6)	5.8 (1.8)	6.4 (1.8)	
Mean (SD)	–3.5 (1.9)	–0.1 (1.8)	–1.9 (2.5)	

mTDS = modified Teacher's Drooling Scale; PP = per protocol; SD = standard deviation.

Source: FH-00-01 Clinical Study Report.[6]

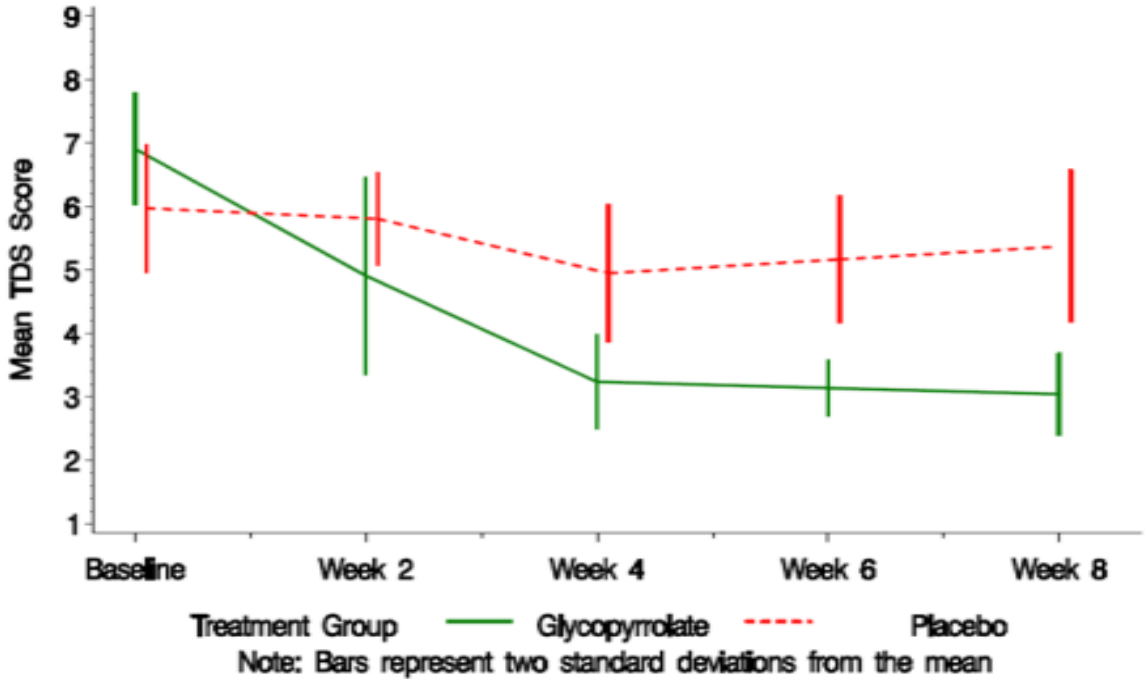
Table 10: Summary of mTDS Responder Rates Over Weeks, Study FH-00-01 (PP Population)

	Total N	Responder rate (percentage showing ≥ change on mTDS)	
		n (%)	P value
Week 2			
Glycopyrrolate	19	7 (37%)	0.005
Placebo	17	0	
Week 4			
Glycopyrrolate	19	10 (53%)	0.007
Placebo	17	2 (12%)	
Week 6			
Glycopyrrolate	19	10 (53%)	0.002
Placebo	17	1 (6%)	

mTDS = modified Teacher's Drooling Score; PP = per protocol.

Source: FH-00-01 Clinical Study Report.[6]

Figure 2: Mean mTDS Score From Baseline to Week 8 for Both Glycopyrrolate and Placebo Groups (Study FH-00-01)



Source: FH-00-01 Clinical Study Report.[6]

No subgroup analyses pertaining to the subgroups identified in the systematic review protocol were reported.

Health-Related Quality of Life

Although no HRQoL measures were included in Study FH-00-01, treatment satisfaction was assessed using caregiver and physician global assessment. With respect to the global assessment conducted at week 8, 19 (100%) parents or caregivers of glycopyrrolate-treated patients versus nine (56%) parents or caregivers of placebo-treated patients agreed that the treatment was "worthwhile," representing a statistically significant difference (P = 0.002). Similarly, 16 (84%) of physicians in the glycopyrrolate group versus seven (41%) in placebo group agreed that the treatment was "worthwhile," which was also a statistically significant difference (P = 0.014). In each measured instance, both the physician and the parent/caregiver assessed glycopyrrolate to be superior to placebo for control of drooling. Detailed results of the global assessment at week 8 are present in Table 11.

Table 11: Summary of Global Assessments From Study FH-00-01

Assessment tool and assessor	Worthwhile?	Glycopyrrolate	Placebo	Total
Study medication				
Physician	Agree?	16 (84%)	7 (41%)	23 (64%)
	N	19	17	36
	Fisher exact test	P = 0.014		
Parent or caregiver	Agree?	19 (100%)	9 (56%)	28 (80%)
	N	19	16	35
	Fisher exact test	P = 0.002		

Note: "Agree" represents both "Strongly agree" and "Agree."

Source: FH-00-01 Clinical Study Report.[6]

Reduction in Salivary Production

Reduction in salivary production was identified as an efficacy outcome of interest in the systematic review protocol, however, this outcome was not assessed in the clinical trial included in this review.

Reduction in Unwanted Symptoms

Reduction in unwanted symptoms associated with excessive drooling (such as skin chafing, *Candida albicans*, or odour) was identified as an efficacy outcome of interest in the systematic review protocol. This outcome was not assessed in the clinical trial included in this review.

Harms

Only those harms identified in the review protocol are reported below. See Table 12 for detailed harms data.

Adverse Events

In Study FH-00-01, all 20 patients treated with glycopyrrolate experienced AEs, of which eight patients (40%) had mild AEs, seven (35%) had moderately severe events, and five (25%) had severe AEs. Of these severe AEs, the most common was constipation, which was reported in 15% of patients. Sixteen patients (89%) in the placebo group experienced AEs, and all were mild or moderate in severity. The most common AEs were GI in nature: constipation, diarrhea, vomiting, and dry mouth.

Serious Adverse Events

SAEs occurred infrequently. In Study FH-00-01, one patient in the glycopyrrolate group experienced one SAE of generalized tonic-clonic seizure activity followed by generalized convulsions post-treatment.

Withdrawals Due to Adverse Events

In Study FH-00-01, two patients discontinued the study drug permanently because of AEs, one in each of the study groups. In the glycopyrrolate group, the patient experienced moderate abdominal distension. In the placebo group, aggravated constipation, dry mouth, flushing, and aggression, as well as mild AEs of disturbance in attention and somnolence, were the cause of withdrawal.

Mortality

No deaths were reported in Study FH-00-01.

Notable Harms

The CDR systematic review protocol identified GI and respiratory AEs as being of particular interest. In terms of GI AEs, in Study FH-00-01, the glycopyrrolate group had 17 (85%) patients with GI events, while the placebo group had nine patients (50%) with GI events. Of these, four (20%) patients in the glycopyrrolate group reported severe GI AEs compared with no patients in the placebo group. The most common GI complaints in the glycopyrrolate and placebo groups respectively were constipation (seven [35%] versus three [17%]), diarrhea (three [15%] versus four [23%]), vomiting (eight [40%] versus two [11%]), and dry mouth (eight [40%] versus two [11%]).

Study FH-00-01 reported 14 (73%) respiratory AEs, nine (45%) in the glycopyrrolate group and five (28%) in the placebo group. Nasal congestion was the most common condition in this category, with six (30%) and two (11%) cases in the respective study groups.

Table 12: Summary of Harms for Study FH-00-01 (Safety Population)

	Pivotal study (FH-00-01)	
AEs	**Glycopyrrolate (1 mg /5 mL) (N = 20)**	**Placebo (N = 18)**
Patients with > 0 AEs, N (%)	20 (100%)	16 (88%)
Most common AEs[a]		
Any gastrointestinal[a]	17 (85%)	9 (50%)
Constipation	7 (35%)	3 (17%)
Diarrhea	3 (15%)	4 (23%)
Vomiting	8 (40%)	2 (11%)
Dry mouth	8 (40%)	2 (11%)
Any psychiatric	6 (30%)	4 (23%)
Mood altered	2 (10%)	2 (11%)
Aggression	1 (5%)	1 (6%)
Restlessness	1 (5%)	2 (11%)
Any infections and infestations	6 (30%)	5 (28%)
Sinusitis	2 (15%)	1 (6%)
Upper respiratory tract infection	3 (15%)	0
Any respiratory, thoracic, and mediastinal disorders[a]	9 (45%)	5 (28%)
Nasal congestion	6 (30%)	2 (11%)
Any investigations	3 (15%)	3 (17%)
Heart rate increased	2 (10%)	1 (6%)
Any nervous system disorder	8 (40%)	8 (45%)
Convulsion	1 (5%)	1 (6%)
Disturbance in attention	1 (5%)	3 (17%)
Headache	3 (15%)	1 (6%)
Somnolence	4 (20%)	5 (28%)
Any renal and urinary disorders	5 (25%)	1 (6%)

AEs	Pivotal study (FH-00-01)	
	Glycopyrrolate (1 mg /5 mL) (N = 20)	Placebo (N = 18)
Urinary retention	3 (15%)	0
Any skin and subcutaneous tissue disorders	3 (15%)	2 (12%)
Rash	1 (5%)	2 (12%)
Any general disorders and administration site conditions	4 (20%)	5 (28%)
Pyrexia	3 (15%)	5 (28%)
Any vascular disorders	6 (30%)	3 (17%)
Flushing	6 (30%)	3 (17%)
Patients with > 0 SAEs, N (%)	1 (5%)	0
Most common SAEs[b]		
Tonic/clonic seizure	1 (5%)	
WDAEs		
WDAEs, N (%)	1 (5%)	
Deaths		
Number of deaths, N (%)	0	

AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Identified as notable harms in the CDR review protocol.

[b] AEs occurring with frequency of 5% or more.

Source: FH-00-01 Clinical Study Report.[6]

Critical Appraisal

Internal Validity

In both study groups of Study FH-00-01, there was a high proportions of patients (> 80%) who completed the eight-week, double-blind treatment period. However, 13 of the 18 (75%) completers in the glycopyrrolate group missed one or more doses of study drug, compared with seven of 15 (44%) completers in the placebo group. Overall, the study patients should have received 168 doses in total; missing doses would mean that some patients had not received optimal treatment dosages. Therefore, there could be a bias leading to an underestimation of treatment effect in favour of glycopyrrolate.

The high incidence of AEs (e.g., constipation, vomiting, and dry mouth) in patients in the glycopyrrolate group, or lack of efficacy in patients who received placebo, could have sacrificed patient (or their caregiver) blinding of treatment. This potential unblinding may have introduced bias in outcome measures, specifically the subjective scales of drooling severity and frequency (i.e., mTDS). Further, the validity of the mTDS is not well established. The clinical expert consulted for this review suggested that drooling outcome measures that are clinically meaningful focus more on psychosocial outcomes, and less on the measurable quantities of saliva produced. When such quantification is desirable, an objective measure, such as the weight of drool bibs or cotton swabs, might be preferable to subjective measures such as the mTDS. Further, four patients had previously taken antidrooling drugs. Two patients (10%) in the glycopyrrolate group had tried scopolamine patches and two (11%) in the placebo group had tried Robinul (another glycopyrrolate formulation). This experience with other anticholinergic medications may have affected

blinding as patients and caregivers would have already been familiar with the expected drooling outcomes and AEs.

Nevertheless, the magnitude of difference between treatment groups in terms of the percentage decrease in the scores was recognized as both statistically and clinically significant, given the relatively small sample size. The PP analysis results were generally consistent with the ITT analysis results. It is unlikely that such a substantial difference could be attributable to random effect or any other factors except for the treatment.

Randomization procedures appeared to be adequate given that the baseline characteristics between the two treatment groups were roughly comparable in each study. Further, the washout period of Study FH-00-01 controlled for any potential confounders that may have been introduced by previous treatment; patients who were taking glycopyrrolate before participation in the study discontinued it within approximately 24 hours prior to baseline, which began on day 8 before randomization.

Sample size calculations were based on a rational anticipated mean change from baseline of 2.4 mTDS units (in the treatment group) and 1.0 units (in the placebo group), even though the FDA has deemed a three unit change to be their definition of a responder. The percentage of patients with at least a three unit improvement on mTDS scores was statistically significant. Therefore, insufficient sample size was perhaps an issue for other secondary outcome measures. The relatively a small sample size and short duration of study period would have definitely increased the uncertainty in the assessment of drug-related severe AEs. Although a change of three or more units on the mTDS is considered meaningful by the FDA, no MCID for the mTDS was identified in the literature.

No subgroup analyses identified in the CDR review protocol were conducted.

External Validity

No Canadian patients were included in Study FH-00-01. Patients in the trial met clinical criteria for severe drooling. The study included mentally impaired patients and those reliant on feeding tubes. In short, the patient population was broadly reflective of the relevant clinical populations for this drug. The definition of severity of drooling was profuse in the absence of treatment such that clothing became damp on most days (i.e., a score of 6 to 9 according to mTDS); however, in 'real world' practice, it is likely that the treatment effect as observed may not be generalizable to those patients with moderate drooling (i.e., a score of 4 to 5 according to mTDS).

In terms of patient characteristics, the majority of patients (78% to 95% in Study FH-00-01) took multiple concomitant medications, which is reflective of the greater CP population.[32] The types of medication taken, muscle relaxants, pain killers, and stool softeners, is also representative of the greater CP patient population. In Study FH-00-01, the majority of patients (75%) were affected by CP as recognized with severe drooling based on the inclusion criteria (e.g., bibs, wet swabs). Therefore, the treatment effect observed in the trial would represent a population with severe drooling caused primarily by CP and an age range of three to 16 years of age. Since the study excluded patients who used botulinum toxin in the past 10 months prior to baseline, the treatment effect by using glycopyrrolate as an add on to existing therapies remained unknown.

The dose and administration of glycopyrrolate was appropriate and relevant in Study FH-00-01, which employed the four-week titration procedure recommended by the sponsor for establishing the appropriate dose, and dose strength was within the range specified in the

Product Monograph.[26] The optimal doses were within the range specified by Health Canada.

No studies identified provided direct comparative evidence for glycopyrrolate. No indirect evidence was submitted by the sponsor. An independent literature search for indirect evidence conducted by CADTH did not identify any evidence that met the inclusion criteria of the CDR review protocol. Therefore, the benefit of glycopyrrolate compared with other treatments for severe drooling used in Canadian clinical practice is unknown.

The study included in the CDR review was of relatively short duration given that treatment with glycopyrrolate is anticipated to be on a chronic basis. Study FH-00-01 was eight weeks in duration and while this duration may be adequate to detect a response to treatment, the long-term benefit of glycopyrrolate remains uncertain.

Indirect Evidence

No indirect evidence was submitted by the sponsor. An independent literature search for indirect evidence conducted by CADTH did not identify any evidence that met the inclusion criteria of the CDR review protocol.

Other Relevant Studies

Long-Term Safety Study (Sc-GLYCO-06-01)

Methods

A six-month, multi-centre, open-label safety study (Sc-GLYCO-06-01) was identified from the sponsor's submission. This single-arm study provides information on the long-term efficacy and safety of oral glycopyrrolate liquid (1 mg/5 mL) for the treatment of chronic, moderate to severe drooling in pediatric patients with CP or other neurologic conditions. After a screening visit, patients entered a washout period (day –14 to day –3) followed by a two-day baseline period, and a four-week dose titration period where the optimal maintenance dose of glycopyrrolate was identified per patient. Patients then continued the optimal dose of glycopyrrolate for 24 weeks.

The primary objective of Study Sc-GLYCO-06-01 was to assess the safety of oral glycopyrrolate liquid given chronically to pediatric patients ages 3 through 18 years with chronic, moderate to severe drooling associated with CP or other neurologic conditions. The secondary objective of relevance to this review was to evaluate the continued efficacy of glycopyrrolate liquid for the management of chronic, moderate to severe drooling in this patient population.

Study Sc-GLYCO-06-01 took place between April 3, 2007 and May 30, 2008. Results were stratified by patients' previous exposure to glycopyrrolate (e.g., naive or non-naive), where naive patients were defined as patients who had not received glycopyrrolate treatment for drooling within three months before starting glycopyrrolate liquid in the study. Therefore, results for Study Sc-GLYCO-06-01 will be presented according to patients' previous exposure to glycopyrrolate. It is unclear if patients were recruited from the FH-00-01 trial.

Patient Eligibility Criteria

Patients were eligible for enrolment in Study Sc-GLYCO-06-01 if they were between three to 18 years of age, weighed at least 13 kg, and had a diagnosis of CP and/or intellectual

disability or any other neurologic impairment or condition (cognitively capable and cognitively impaired patients could be enrolled). Patients were included in the study if they had chronic drooling in the absence of treatment to the extent that the chin or clothing becomes wet most days by confirming an mTDS score greater than or equal to 5, and if they had parents or caregivers who were willing and capable of administering medications. Patients were excluded if they used glycopyrrolate within approximately 24 hours prior to baseline, and if they had received injections with intrasalivary gland botulinum toxin within 10 months prior to baseline. Patients who used intraoral devices or prosthetics for the treatment of drooling within one week of baseline, or received acupuncture for the treatment of drooling within three months prior to baseline were excluded.

Population

Study Sc-GLYCO-06-01 included patients from 28 sites across the US.

The mean age of patients in Study Sc-GLYCO-06-01 was 11 years. Male patients were overrepresented in the naive group (60.7% in the naive group versus 49.1% in the non-naive group). The majority of patients were white (71.5%), had intellectual disability (90.5%), and had speech impairment (97.8%). Approximately 66% of patients had oral feeding problems and 51% used a tube for feeding. Approximately 70% of patients had CP.

Table 13: Summary of Baseline Characteristics

	Naive (N = 84)	Non-naive (N = 53)	Total (N = 137)
Age, mean years (SD)	10.9 (4.38)	11.1 (4.35)	11.0 (4.35)
Age group (years)			
≥ 3 to ≤ 6	17 (20.2%)	9 (17.0%)	26 (19.0%)
> 6 to ≤ 10	20 (23.8%)	16 (30.2%)	36 (26.3%)
> 10 to ≤ 14	26 (31.0%)	13 (24.5%)	39 (28.5%)
> 14 to ≤ 18	21 (25.0%)	15 (28.3%)	36 (26.3%)
Male, n (%)	51 (60.7%)	26 (49.1%)	77 (56.2%)
Race			
White	61 (72.6%)	37 (69.8%)	98 (71.5%)
Black or African-American	19 (22.6%)	10 (18.9%)	29 (21.2%)
American Indian or Alaska Native	1 (1.2%)	0	1 (0.7%)
Asian	0	4 (7.5%)	4 (2.9%)
Other	3 (3.6%)	2 (3.8%)	5 (3.6%)
Intellectual disability, n (%)	75 (89.3%)	49 (92.5%)	124 (90.5%)
Speech impairment, n (%)	81 (96.4%)	53 (100.0%)	134 (97.8%)
Oral feeding problems, n (%)	49 (58.3%)	42 (79.2%)	91 (66.4%)
Uses tube for feeding, n (%)	35 (41.7%)	35 (66.0%)	70 (51.1%)
Patient has cerebral palsy, n (%)	55 (65.5%)	41 (77.4%)	96 (70.1%)

SD = standard deviation.

Source: Clinical Study Report for Study Sc-GLYCO-06-01.[33]

Interventions

All patients were treated with oral glycopyrrolate liquid (1 mg/5 mL) for 24 weeks. Titration to the optimal or maximal dose was performed using a dose titration schedule based on weight. Titration started at 0.02 mg/kg per dose three times daily and was increased in 0.02 mg/kg per dose increments three times daily every five to seven days during the first four weeks until an optimal individual response or a maximum of 0.1 mg/kg three times daily or 3 mg three times daily was attained. Oral glycopyrrolate liquid was administered at the following times by a parent, caregiver, or school nurse: 7 a.m. to 8 a.m., 1 p.m. to 2 p.m., and 7 p.m. to 8 p.m. at least one hour before or one hour after a meal.

Any medication with an anticholinergic effect and all pharmacologic and nonpharmacologic treatments for sialorrhea (except glycopyrrolate liquid), were prohibited during the study. Use of concomitant medication for underlying conditions other than sialorrhea was permitted.

Outcomes

The primary efficacy outcome was patient response status, based on change from baseline to week 24 evaluated by the mTDS, where responders were any patient with at least a three point decrease from baseline in mean mTDS rating. The mTDS evaluated the severity and frequency of drooling using a nine-point scale, described in Appendix 3.

Secondary outcomes included the VAS for the assessment of the extent of drooling, and global assessments by the parent or caregiver.

The VAS was 10 cm in length and allowed parents or caregivers to assess the extent of drooling between 0 cm (normal) to 10 cm (extremely wet).

The global assessment of the overall treatment by the parent/caregiver was performed using a five-point scale corresponding to the following statement: “This is a worthwhile treatment.” The response options were as follows: 1 = strongly agree, 2 = agree, 3 = neutral, 4 = disagree, and 5 = strongly.

Harms outcomes assessed included AEs, SAEs, withdrawals due to adverse events, and deaths.

Statistical Analysis

Results were summarized using descriptive statistics and using frequency and percentage for discrete variables. Results were presented with two-sided CIs with a type I error of 0.05. No adjustments for multiple comparisons or multiplicity were made.

Missing data for patients who dropped out due to lack of efficacy had their data imputed using worst observation carried forward (WOCF) methodology. Patients who dropped out for reasons other than lack of efficacy had their missing data imputed using last observation carried forward (LOCF) methodology.

All analyses in Study Sc-GLYCO-06-01 were conducted using the ITT population. The ITT population included all patients who received any study drug.

Patient Disposition

A total of 137 patients (naive = 84; non-naive = 53) were included in the ITT population. Approximately 25% of patients from the total study population discontinued the trial, with most study discontinuations occurring in naive patients (naive = 33.3%; non-naive = 11.3%). Discontinuations from the study were most commonly attributed to AEs (naive = 14.3%; non-naive = 3.8%).

Table 14: Patient Disposition

	Sc-GLYCO-06-01		
	Naive	Non-naive	Total
Enrolled, N	99	61	160
Screen failure, N	15	8	23
Completed study, N (%)	56 (66.7%)	47 (88.7%)	103 (75.2%)
Discontinued, N (%)	28 (33.3%)	6 (11.3%)	34 (24.8%)
Adverse events	12 (14.3%)	2 (3.8%)	14 (10.2%)
Patient/parent decision	4 (4.8%)	1 (1.9%)	5 (3.6%)
Lost to follow-up	3 (3.6%)	0	3 (2.2%)
Death	2 (2.4%)	1 (1.9%)	3 (2.2%)
Failed to meet entry criteria	2 (2.4%)	0	2 (1.5%)
Lack of efficacy	1 (1.2%)	1 (1.9%)	2 (1.5%)
Investigator decision	2 (2.4%)	0	2 (1.5%)
Patient not compliant with study requirements	2 (2.4%)	0	2 (1.5%)
Other	0	1 (1.9%)	1 (0.7%)
ITT, N	84	53	137

ITT = intention to treat.

Source: Clinical Study Report for Study Sc-GLYCO-06-01.[33]

Exposure to Study Treatments

The mean total dose was 606.4 mg (SD = 446.65 mg) in the naive group, and 847.4 mg (SD = 424.19 mg) in the non-naive group. The mean daily dose was 0.1424 mg/kg (SD = 0.06596 mg/kg) in the naive group, and 0.1745 mg/kg (SD = 0.05905 mg/kg) in the non-naive group. Approximately half of patients (48.8% in the naive group and 54.7% in the non-naive group) were exposed to mean daily dose range of 0.1 mg/kg or greater or 0.2 mg/kg or less.

Efficacy

Modified Teacher's Drooling Scale

The proportion of responders based on the mTDS was 48.1% (95% CI, 36.9% to 59.2%) in the naive group and 58.5% (95% CI, 45.2% to 71.8%) in the non-naive group at week 24 (Table 15). The three point criterion is consistent with guidance from the FDA. The greatest proportion of responders were those treated with doses in the following ranges: 0.04 mg/kg or greater to less than 0.06 mg/kg and 0.06 mg/kg to less 0.08 mg/kg (Table 16).

Patients in both the naive and non-naive groups improved in the mTDS with reductions in the percentage of patients in the mTDS combined categories for profuse, severe, and moderate drooling after 24 weeks of treatment (Table 17). At baseline, 21.0% and 22.6% of patients in the naive and non-naive groups, respectively, were categorized as having profuse drooling, compared with 2.5% and 1.9% at week 24. Similarly, at baseline, 34.5% and 39.6% of patients in the naive and non-naive groups, respectively, were categorized as having severe drooling, compared with 7.5% and 9.4% at week 24. According to the mTDS assessment, 13.8% and 17% of patients in the naive and non-naive groups, respectively, were no longer drooling at the end of the study.

Table 15: Proportion of Responders According to the mTDS (ITT)

	Naive (N = 84)	Non-naive (N = 53)	Total (N = 137)
Week 24			
Responder	37 (48.1%)	31 (58.5%)	68 (52.3%)
Nonresponder	40 (51.9%)	22 (41.5%)	62 (47.7%)
Missing	7	0	7
95% CI[a]	(36.9% to 59.2%)	(45.2% to 71.8%)	(43.7% to 60.9%)

CI = confidence interval; ITT = intention to treat; mTDS = modified Teacher's Drooling Scale; PP = per protocol.

Note: Percentages were calculated using the number of patients with non-missing values within each stratum. Each patient was classified as a responder or a nonresponder according to the change in their mean mTDS rating (rounded to the nearest integer) from baseline to week 24 or exit visit. Any patient with at least a three-point decrease from baseline in mean mTDS rating was classified a responder.

[a] Two-sided 95% CI using normal approximation to the binomial for the percentage of responders.

Source: Clinical Study Report for Study Sc-GLYCO-06-01.[33]

Table 16: Proportion of Responders According to the mTDS at Each Dose Level (ITT)

	Maximum dose (N = 137)		Last dose (N – 127)	
Dose range	**Responder (N = 68)**	**Nonresponder (N = 62)**	**Responder (N = 68)**	**Nonresponder (N = 62)**
< 0.02 mg/kg	1 (1.5%)	4 (6.4%)	2 (2.9%)	9 (14.5%)
≥ 0.02 mg/kg to < 0.04 mg/kg	7 (10.3%)	6 (9.7%)	14 (20.6%)	12 (19.4%)
≥ 0.04 mg/kg to < 0.06 mg/kg	19 (27.9%)	22 (35.5%)	23 (33.8%)	18 (29.0%)
≥ 0.06 mg/kg to < 0.08 mg/kg	21 (30.9%)	17 (27.4%)	19 (27.9%)	12 (19.4%)
≥ 0.08 mg/kg to < 0.1 mg/kg	16 (23.5%)	7 (11.3%)	7 (10.3%)	9 (14.5%)
≥ 0.1 mg/kg	4 (5.9%)	6 (9.7%)	3 (4.4%)	2 (3.2%)

ITT = intention to treat; mTDS = modified Teacher's Drooling Scale.

Source: Clinical Study Report for Study Sc-GLYCO-06-01.[33]

Table 17: mTDS (ITT)

	Naive (N = 84)	Non-naive (N = 53)	Total (N = 137)
Baseline			
1 = Dry (never drools)	0	0	0
2 = Mild only the lips are wet; occasionally	3 (3.7%)	2 (3.8%)	5 (3.7%)
3 = Mild only the lips are wet; frequently	7 (8.6%)	1 (1.9%)	8 (6.0%)
4 = Moderate: wet on the lips and chin; occasionally	2 (2.5%)	6 (11.3%)	8 (6.0%)
5 = Moderate: wet on the lips and chin; frequently	24 (29.6%)	11 (20.8%)	35 (26.1%)
6 = Severe: drools to the extent that clothing becomes damp; occasionally	13 (16.0%)	4 (7.5%)	17 (12.7%)
7 = Severe: drools to the extent that clothing becomes damp; frequently	15 (18.5%)	17 (32.1%)	32 (23.9%)
8 = Profuse: clothing, hands, tray, and objects become wet; occasionally	6 (7.4%)	5 (9.4%)	11 (8.2%)
9 = Profuse: clothing, hands, tray, and objects become wet; frequently	11 (13.6%)	7 (13.2%)	18 (13.4%)
Missing	3	0	3
Week 24/Exit Visit[a]			
1 = Dry (never drools)	11 (13.8%)	9 (17.0%)	20 (15.0%)
2 = Mild only the lips are wet; occasionally	21 (26.3%)	17 (32.1%)	38 (28.6%)
3 = Mild only the lips are wet; frequently	16 (20.0%)	11 (20.8%)	27 (20.3%)
4 = Moderate: wet on the lips and chin; occasionally	16 (20.0%)	5 (9.4%)	21 (15.8%)
5 = Moderate: wet on the lips and chin; frequently	8 (10.0%)	5 (9.4%)	13 (9.8%)
6 = Severe: drools to the extent that clothing becomes damp; occasionally	4 (5.0%)	1 (1.9%)	5 (3.8%)
7 = Severe: drools to the extent that clothing becomes damp; frequently	2 (2.5%)	4 (7.5%)	6 (4.5%)
8 = Profuse: clothing, hands, tray, and objects become wet; occasionally	0	0	0
9 = Profuse: clothing, hands, tray, and objects become wet; frequently	2 (2.5%)	1 (1.9%)	3 (2.3%)
Missing	4	0	4

[a] Missing values at week 24/exit visit were imputed using worst observation carried forward if the patient discontinued due to lack of efficacy or last observation carried forward if the value was missing for any other reason.

Source: Clinical Study Report for Study Sc-GLYCO-06-01.[33]

VAS for the Extent of Drooling

The VAS assessment for the extent of drooling showed a mean score of 6.57 and 6.54 for patients in the naive and non-naive groups, respectively, at baseline and 3.25 and 3.15 at week 24, indicating an approximate change in score of three units.

Table 18: VAS Assessment for Extent of Drooling (ITT)

	Naive (N = 84)	Non-naive (N = 53)	Total (N = 137)
Baseline, n	83	53	136
Mean (SD)	6.57 (2.305)	6.54 (2.413)	6.56 (2.339)
Median	6.90	6.90	6.90
Missing	1	0	1
Week 24/Exit Visit[a], n	80	53	133
Mean (SD)	3.25 (2.259)	3.15 (2.133)	3.21 (2.202)
Median	2.95	2.70	2.80
Missing	4	0	4

ITT = intention to treat; SD = standard deviation; VAS = Visual Analogue Scale.

[a] Missing values at week 24/exit visit were imputed using worst observation carried forward if the patient discontinued due to lack of efficacy or last observation carried forward if the value was missing for any other reason.

Source: Clinical Study Report for Study Sc-GLYCO-06-01.[33]

Global Assessments by the Parent or Caregiver

At the end of the study, 85.7% of parents or caregivers in the naive group and 80.4% of parents or caregivers in the non-naive group agreed or strongly agreed with the statement: "This is a worthwhile treatment."

Table 19: Dichotomized Parent or Caregiver Global Assessment (ITT)

	Naive (N = 84)	Non-naive (N = 53)	Total (N = 137)
Parent/caregiver's assessment at week 24			
Responder	60 (85.7%)	41 (80.4%)	101 (83.5%)
Nonresponder	10 (14.3%)	10 (19.6%)	20 (16.5%)
95% CI	(77.5% to 93.9%)	(69.5% to 91.3%)	(76.9% to 90.1%)

CI = confidence interval; ITT = intention to treat.

Note: The responses assessed the statement: "This is a worthwhile treatment." A dichotomous global assessment was created with the categories 'responder' (strongly agree and agree responses aggregated) and 'nonresponder' (neutral, disagree, and strongly disagree response).

[a] Two-sided 95% CI using normal approximation to the binomial for the percentage of responders.

Source: Clinical Study Report for Study Sc-GLYCO-06-01.[33]

Harms

In Study Sc-GLYCO-06-01, 90.5% of patients in the naive group and 86.8% of patients in the non-naive group experienced an AE (Table 20). In both the naive and non-naive groups, the most common AEs were constipation, vomiting, and diarrhea. In general, the incidence of AEs appeared to increase as the dose of glycopyrrolate increased. Fourteen patients experienced 20 SAEs. Treatment-emergent SAEs were most commonly attributed to pneumonia and are presented in Table 20. No deaths occurred during the study, however, three patients died within 30 days of the last dose of the study drug.

Table 20: Harms (ITT)

	Naive (N = 84)	Non-naive (N = 53)	Total (N = 137)
AEs[a]			
Patients with > 0 AEs, N (%)	76 (90.5%)	46 (86.8%)	122 (89.1%)
Gastrointestinal disorders	38 (45.2%)	30 (56.6%)	68 (49.6%)
Constipation	17 (20.2%)	11 (20.8%)	28 (20.4%)
Vomiting	12 (14.3%)	12 (22.6%)	24 (17.5%)
Diarrhea	15 (17.9%)	9 (17.0%)	24 (17.5%)
Dry mouth	8 (9.5%)	7 (13.2%)	15 (10.9%)
Dry lips	1 (1.2%)	4 (7.5%)	5 (3.6%)
Infections and infestations	40 (47.6%)	28 (52.8%)	68 (49.6%)
Otitis media	4 (4.8%)	8 (15.1%)	12 (8.8%)
Urinary tract infection	5 (6.0%)	6 (11.3%)	11 (8.0%)
Upper respiratory tract infection	8 (9.5%)	3 (5.7%)	11 (8.0%)
Pneumonia	3 (3.6%)	4 (7.5%)	7 (5.1%)
Gastroenteritis, viral	6 (7.1%)	0	6 (4.4%)
Respiratory, thoracic, and mediastinal disorders	20 (23.8%)	14 (26.4%)	34 (24.8%)
Nasal congestion	8 (9.5%)	7 (13.2%)	15 (10.9%)
Upper respiratory tract congestion	2 (2.4%)	4 (7.5%)	6 (4.4%)
Nervous system disorders	17 (20.2%)	14 (26.4%)	31 (22.6%)
Convulsion	7 (8.3%)	4 (7.5%)	11 (8.0%)
Somnolence	1 (1.2%)	6 (11.3%)	7 (5.1%)
TREATMENT-EMERGENT SAEs			
Patients with > 0 SAEs, N (%)	4 (4.8%)	4 (7.5%)	8 (5.8%)
Pneumonia	1 (1.2%)	2 (3.8%)	3 (2.2%)
Urinary tract infection	0	1 (1.9%)	1 (0.7%)
Cellulitis	1 (1.2%)	0	1 (0.7%)
Otitis media	1 (1.2%)	0	1 (0.7%)
Therapeutic agent toxicity	1 (1.2%)	0	1 (0.7%)
Dehydration	1 (1.2%)	0	1 (0.7%)
Convulsion	0	1 (1.2%)	1 (0.7%)
Hydrocephalus	0	1 (1.2%)	1 (0.7%)
DEATHS	0	0	0

AE = adverse event; ITT = intention to treat; SAE = severe adverse event.

[a] Frequency > 6%.

Source: Clinical Study Report for Study Sc-GLYCO-06-01.[33]

Table 21: AEs by Dose Group (ITT)

	< 0.1 mg/kg (N = 29)	≥ 0.1 to ≤ 0.2 mg/kg (N = 70)	> 0 .2 mg/kg (N = 38)
AEs[a]			
Patients with > 0 AEs, N (%)	24 (82.8%)	63 (90.0%)	35 (92.1%)
Gastrointestinal disorders	11 (37.9%)	39 (55.7%)	18 (47.4%)
Constipation	7 (24.1%)	17 (24.3%)	4 (10.5%)
Diarrhea	5 (17.2%)	13 (18.6%)	6 (15.8%)
Vomiting	4 (13.8%)	13 (18.6%)	7 (18.4%)
Dry Mouth	1 (3.4%)	8 (11.4%)	6 (15.8%)
Infections and infestations	9 (31.0%)	36 (51.4%)	23 (60.5%)
Otitis media	1 (3.4%)	7 (10.0%)	4 (10.5%)
Urinary tract infection	3 (10.3%)	4 (5.7%)	4 (10.5%)
Upper respiratory tract infection	1 (3.4%)	7 (10.0%)	3 (7.9%)
Influenza	1 (3.4%)	2 (2.9%)	4 (10.5%)
Pneumonia	0	4 (5.7%)	3 (7.9%)
Pharyngitis streptococcal	1 (3.4%)	3 (4.3%)	3 (7.9%)
Nasopharyngitis	1 (3.4%)	1 (1.4%)	3 (7.9%)
Ear infection	1 (3.4%)	0	3 (7.9%)
Respiratory, thoracic, and mediastinal disorders	5 (17.2%)	18 (25.7%)	11 (28.9%)
Nasal congestion	3 (10.3%)	8 (11.4%)	4 (10.5%)
Epistaxis	1 (3.4%)	3 (4.3%)	3 (7.9%)
Nervous system disorders	9 (31.0%)	17 (24.3%)	5 (13.2%)
Convulsion	4 (13.8%)	5 (7.1%)	2 (5.3%)
Somnolence	0	6 (8.6%)	1 (2.6%)
Headache	2 (6.9%)	2 (2.9%)	2 (5.3%)
General disorders and administration site	4 (13.8%)	15 (21.4%)	9 (23.7%)
conditions	2 (6.9%)	11 (15.7%)	7 (18.4%)
Pyrexia	2 (6.9%)	5 (7.1%)	1 (2.6%)
Irritability	11 (37.9%)	39 (55.7%)	18 (47.4%)

AE = adverse event; ITT = intention to treat.

[a] Frequency > 6%.

Source: Clinical Study Report for Study Sc-GLYCO-06-01.[33]

Critical Appraisal

Study Sc-GLYCO-06-01 was limited with respect to the open-label design of the study. All patients were treated with oral glycopyrrolate liquid and results were stratified by treatment-naive versus non-naive status. The absence of an active comparator reduces the ability to compare the efficacy of glycopyrrolate with alternative drugs that are used in clinic. Study Sc-GLYCO-06-01 was not performed in a Canadian setting as all patients were recruited from the US. Patients were eligible for the study regardless of prior treatment with glycopyrrolate liquid and results were stratified for naive and non-naive patients. The inclusion of non-naive patients introduces the possibility of participation bias as patients who were previously had a favourable response to glycopyrrolate liquid may be more likely to enter the study compared to patients who did not have a favourable response. This is

unlikely to be an issue in patients in the naive group. Baseline characteristics were generally balanced between the naive and non-naive patients with the exception of gender, as male patients were overrepresented in the naive group (60.7% in the naive group verses 49.1% in the non-naive group). The primary efficacy evaluation was based on the mTDS, and while this scale has been used in trials and the FDA has specified guidance on its use, the mTDS is not a validated scale.

Summary of Study Sc-GLYCO-06-01

Study Sc-GLYCO-06-01 was a 24-week, multi-centre, open-label safety study designed to assess the long-term efficacy and safety of oral glycopyrrolate liquid (1 mg/5 mL) for the treatment of chronic, moderate to severe drooling in pediatric patients with CP or other neurologic conditions. Patients enrolled in Study Sc-GLYCO-06-01 could be naive or non-naive with respect to prior treatment with oral glycopyrrolate liquid. The baseline characteristics of patients in the Sc-GLYCO-06-01 study were generally similar to patients in the FH-00-01 study. Key limitations of Study Sc-GLYCO-06-01 were related to the open-label, single-arm design of the study. Results of the Sc-GLYCO-06-01 study may suggest improvement in drooling based on the mTDS after 24 weeks of treatment with glycopyrrolate liquid. Fewer AEs related to GI and respiratory events were observed in the 24-week Sc-GLYCO-06-01 study compared with the eight-week pivotal trial (FH-00-01), but the higher number of GI AEs in Study FH-00-01 may be artificially inflated due to the small sample size of this study. Overall, efficacy results were aligned with those of Study FH-00-01. No new safety signals arose over the course of the 24-week Sc-GLYCO-06-01 study compared to the eight-week pivotal trial (FH-00-01).

Discussion

Summary of Available Evidence

One phase III RCT was included in the systematic review. Study FH-00-01 (N = 38) was a multi-centre, randomized, double-blind, placebo-controlled, eight-week study conducted at multiple sites in the US and was designed to assess the safety and efficacy of oral glycopyrrolate liquid (1 mg/5 mL) compared with placebo in the management of problem drooling in children with CP or other neurologic conditions. Patients enrolled in this study were between 3 and 16 years of age who exhibited severe drooling. Patients were randomized in a 1:1 ratio to either glycopyrrolate or placebo. The dose of glycopyrrolate was titrated during the first four weeks of the study. The primary outcome was the treatment responder rate and based on the mTDS at week 8 (the change in mTDS score from baseline to week 8 was also reported). Other secondary outcomes of interest to this review included the responders and change from baseline on the mTDS at weeks 2, 4, and 6, and patient or caregiver and physician global assessments.

The other study of relevance to this review was the long-term, open-label, single-arm, study, Sc-GLYCO-06-01. The primary objective of this study was to evaluate the safety of oral glycopyrrolate liquid given chronically to pediatric patients ages 3 through 18 years with chronic, moderate to severe drooling associated with CP or other neurologic conditions. The secondary objectives were to evaluate the continued efficacy of glycopyrrolate.

Interpretation of Results

Efficacy

Overall, results of Study FH-00-01 support glycopyrrolate as an efficacious treatment for reduction of drooling. However, the outcomes upon which these results are based are subjective.

Study FH-00-01 assessed the change in degree of drooling using the mTDS. Results of the FDA-requested primary outcome measure, dichotomized rate of responders, showed that glycopyrrolate was superior to placebo in that more patients in the glycopyrrolate group were considered responders at week 8 than in the placebo group. Differences were also observed in the rate of responders at weeks 2, 4, and 6 in favour of glycopyrrolate. Note that a change in mTDS score of 3 or more is considered clinically meaningful by the FDA, but no MCID was identified in the literature, and this scale has not been validated. The change in mTDS score from baseline to week 8 was also significantly greater in patients treated with glycopyrrolate than in patients treated with placebo.

The mTDS is not well validated, and no MCID was identified in the literature, although the FDA recognizes a three unit change in mTDS as being clinically meaningful. However, the clinical expert consulted for this review had confidence in efficacy studies that rely upon these measures.

Although HRQoL was not specifically measured in Study FH-00-01, treatment satisfaction was measured via global assessment. At week 8 a greater proportion of glycopyrrolate-treated patients than placebo-treated parent/caregivers agreed that the treatment was “worthwhile.” This was also true for the assessment by physicians. However, it is unclear whether this measure was controlled for multiplicity.

Other efficacy outcomes identified in the CDR review protocol included reduction in salivary production and reduction in unwanted symptoms associated with drooling; neither of these outcomes were assessed in the clinical trial included in this review.

Subgroups identified as relevant to this CDR review in consultation with a clinical expert included the nature and severity of the underlying neurologic condition. Study FH-00-01 did not assess the efficacy or safety of glycopyrrolate in either of these subgroups.

Study Sc-GLYCO-06-01 was a 24-week, multi-centre, open-label safety study designed to assess the long-term efficacy and safety of oral glycopyrrolate liquid (1 mg/5 mL) for the treatment of chronic, moderate to severe drooling in pediatric patients with CP or other neurologic conditions. Patients enrolled in Study Sc-GLYCO-06-01 could be naive or non-naive with respect to prior treatment with oral glycopyrrolate liquid. The baseline characteristics of patients in the Sc-GLYCO-06-01 study were generally similar to patients in the FH-00-01 study. The results of Study Sc-GLYCO-06-01 may suggest improvement in drooling based on the mTDS after 24 weeks of treatment with glycopyrrolate liquid. Key limitations of Study Sc-GLYCO-06-01 were related to the open-label, single-arm design of the study.

Harms

A high proportion of patients treated with glycopyrrolate in Study FH-00-01 experienced GI AEs, such as constipation, vomiting, and dry mouth. Other studies consistently show that patients taking glycopyrrolate experienced similar GI AEs, observed across a wide scope of patient profiles, including both adult and pediatric.[5] Few SAE were reported in Study FH-00-01.

Notable harms of interest to this review included GI and respiratory AEs. In terms of GI AEs, in Study FH-00-01, the glycopyrrolate group experienced 17 (85%) events, while the placebo group had nine patients (50%) with GI events. The most common GI complaints were constipation, diarrhea, vomiting, and dry mouth. Nasal congestion was the most common respiratory AE.

Fewer AEs related to GI and respiratory events were observed in the 24-week Sc-GLYCO-06-01 study compared with the eight-week pivotal trial (FH-00-01), but the higher number of GI AEs in Study FH-00-01 may be artificially inflated due to the small sample size of this study. Overall, efficacy results were aligned with those of Study FH-00-01. No new safety signals arose over the course of the 24-week Sc-GLYCO-06-01 study compared to the eight-week pivotal trial (FH-00-01).

Other Considerations

Drooling is a chronic condition. The short time frame of Study FH-00-01 (eight weeks) might not be sensitive to the long-term treatment implications which might manifest as evolving harms or diminished efficacy over time. While this duration of the included study may be adequate to detect a response to treatment, the long-term benefit of glycopyrrolate remains uncertain. The six-month Sc-GLYCO-06-01 study offers some insight, showing sustained efficacy throughout the 24-week period, with a safety profile comparable to that seen in the shorter-term studies.

The FH-00-01 study did not include study sites in Canada.

A gap in evidence is the lack of data demonstrating that treatment with glycopyrrolate oral solution offers a benefit in terms of HRQoL. The clinical expert consulted for this review emphasized the importance of the psychosocial aspect of drooling to patients; this was not captured by any outcome measures in any of the trials. The clinical expert had expressed that treatment goals for this population are both medical and social, with the former having to do with the management of skin maceration, odour, dehydration, speech impairment, and risk of aspiration, and the latter concerning improved family dynamics, reduced caregiver fatigue, and the facilitation of schooling and socialization. This review did not address any of these goals, thus identifying a research gap to be filled. Moreover, neither glycopyrrolate nor any of the drugs in its anticholingeric class address the actual cause of sialorrhea, but rather treat the symptom.

According to the clinical expert, the most commonly used pharmacologic treatment in Canada is botulinum toxin. No direct evidence comparing glycopyrrolate oral solution with botulinum toxin (or any other comparators identified in the review protocol) was identified. The only comparative evidence identified was in a study by Parr et al., where hyoscine served as the comparator to glycopyrronium oral solution.[4] In this study, the degree of drooling was assessed using the DIS and DSFS, which are both subjective, unvalidated measures with no generally accepted MCID. Both hyoscine and glycopyrronium led to statistically significant reductions in drooling based on DIS score from baseline to week 4, however the magnitude of the reduction in DIS score at week 4 was similar between groups. The magnitude of the reduction in DIS was also similar between groups at week 12. However, it is uncertain whether the formulation of glycopyrronium used in this trial is the same as the product under review, and the specific dose of hyoscine was not reported. Further, the relevance of this comparator to treatment for severe drooling in Canada is questionable. According to the clinical expert consulted for this CDR review, hyoscine is not commonly used in Canadian clinical practice; further, hyoscine patches are not commercially available in Canada. No indirect evidence was submitted by the sponsor. An independent literature search for indirect evidence conducted by CADTH did not identify any evidence that met the inclusion criteria of the CDR review protocol. Therefore, the comparative efficacy of glycopyrrolate versus other treatments for severe drooling in this population used in Canada remains unknown. A systematic review by Walshe et al.[8] aimed to evaluate pharmacologic interventions for reducing drooling in children with CP. The interventions included botulinum toxin A, benztropine, and glycopyrrolate. The studies examined herein used a variety of subjective scales, including the mTDS, DIS, and DSFS; the mTDS was also used in Study FH-00-01. The overall conclusion of the systematic review by Walsh and colleagues was that there is insufficient evidence to conclusively evaluate the safety and effectiveness of antidrooling interventions. The clinical expert advising this review suggested that glycopyrrolate is unlikely to replace the leading antidrooling approaches, particularly botulinum toxin. The expert suggested that glycopyrrolate may be used as a complement to other strategies or as an alternative to anticholinergics and acknowledged that it may be used by primary care physicians.

Conclusions

One phase III RCT comparing glycopyrrolate to placebo (FH-00-01) was included in the CDR systematic review of glycopyrrolate oral solution to reduce chronic drooling. Study FH-00-01 demonstrated that in children with neurologic impairments (e.g., CP), orally administered glycopyrrolate is an effective agent for reducing excessive drooling. The responder rate on the mTDS at week 8 was statistically significantly higher in patients treated with glycopyrrolate than placebo. Study FH-00-01 was associated with methodological limitations, including subjective, non-validated outcome measures to assess the change in degree of drooling and potential for unblinding.

A high proportion of patients treated with glycopyrrolate experienced similar GI AEs, such as constipation, vomiting, and dry mouth. SAEs occurred infrequently in Study FH-00-01. No new safety signals arose over the course of the 24-week Sc-GLYCO-06-01 study compared to the eight-week pivotal trial (FH-00-01).

There is no direct or indirect evidence comparing the efficacy or safety of glycopyrrolate oral solution to other treatments for severe drooling used in Canadian clinical practice (atropine, benztropine, botulinum toxin, trihexyphenidyl, or surgical interventions) in children with neurologic conditions.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946 to present) Embase (1974 to present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 8, 2019
Alerts:	Bi-weekly search updates until project completion
Study types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
MeSH	Medical Subject Heading
exp	Explode a subject heading
.ti	Title
.ab	Abstract
.dq	Candidate term word (Embase)
.ot	Original title
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	glycopyrrolate/
2	(Cuvposa* or glycopyrrolate or Sialanar or glycopyrronium or NVA237 or NVA 237 or asecryl or Copyrrolate or Gastrodyn or Glycopyrronium or Lonhala Magnair or Nodapton or NSC250836 or NSC 250836 or NSC251251 or NSC 251251 or NSC 251252 or NSC 251252 or Robinul or Glycate or Glyrx-PF or Seebri or Tarodyl or Tarodyn or Acpan or Qbrexza or ad 237 or ad237 or ahr 504 or ahr504 or "drm 04" or drm04 or enurev or glersa or mobinul or robinal or robinol or sialanar or sroton or strodin or tovanor or V92SO9WP2I or A14FB57V1D).ti,ab,ot,kf,hw,rn,nm.
3	1 or 2
4	sialorrhea/
5	(sialorrhea or hypersalivat* or drool* or polysialia or ptyalism or hypersialorrhea or hyperptyalism or ptyalorrhea or sialism or sialosis or sialorrhoea or saliva*).ti,ab,ot,kf.
6	4 or 5
7	3 and 6
8	7 use medall
9	*glycopyrronium/
10	(Cuvposa* or glycopyrrolate or Sialanar or glycopyrronium or NVA237 or NVA 237 or asecryl or Copyrrolate or Gastrodyn or Glycopyrronium or Lonhala Magnair or Nodapton or NSC250836 or NSC 250836 or NSC251251 or NSC 251251 or NSC 251252 or NSC 251252 or Robinul or Glycate or Glyrx-PF or Seebri or Tarodyl or Tarodyn or Acpan or Qbrexza or ad 237 or ad237 or ahr 504 or ahr504 or "drm 04" or drm04 or enurev or glersa or mobinul or robinal or robinol or seebri or sialanar or sroton or strodin or tovanor).ti,ab,kw,dq.
11	9 or 10
12	exp salivation disorder/
13	sialorrhea or hypersalivat* or drool* or polysialia or ptyalism or hypersialorrhea or hyperptyalism or ptyalorrhea or sialism or sialosis or sialorrhoea or saliva*).ti,ab,kw,dq.
14	12 or 13
15	11 and 14
16	15 use oemezd
17	16 not (conference review or conference abstract).pt.
18	8 or 17
19	remove duplicates from 18

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search terms: Cuvposa OR glycopyrrolate OR NVA237 OR NVA 237	
WHO ICTRP	International Clinical Trials Registry Platform, produced by WHO. Targeted search used to capture registered clinical trials. Search terms: Cuvposa OR glycopyrrolate OR NVA237 OR NVA 237	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	

Grey Literature

Dates for Search:	July 3 to July 8, 2019
Keywords:	Cuvposa, glycopyrrolate, drooling
Limits:	None

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug And Device Regulatory Approvals
- Advisories And Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (Free)
- Internet Search.

Appendix 2: Excluded Studies

Table 22: Excluded Studies

Reference	Reason for exclusion
Arbouw ME, Movig KL, Koopmann M, et al. Glycopyrrolate for sialorrhea in Parkinson disease: a randomized, double-blind, crossover trial. *Neurology*. 2010;74(15):1203-1207.[31]	Comparator group (placebo) not identified in the CDR review protocol
Gronnebech H, Johansson G, Smedebol M, Valentin N. Glycopyrrolate vs. atropine during anaesthesia for laryngoscopy and bronchoscopy. *Acta Anaesthesiol Scand*. 1993;37(5):454-457.[34]	Study population (adults) not identified in the CDR review protocol
Liang CS, Ho PS, Shen LJ, Lee WK, Yang FW, Chiang KT. Comparison of the efficacy and impact on cognition of glycopyrrolate and biperiden for clozapine-induced sialorrhea in schizophrenic patients: a randomized, double-blind, crossover study. *Schizophr Res*. 2010;119(1-3):138-144.[35]	Study population (adults) not identified in the CDR review protocol
Man WH, Colen-de Koning JC, Schulte PF, et al. The Effect of Glycopyrrolate on Nocturnal Sialorrhea in Patients Using Clozapine: A Randomized, Crossover, Double-Blind, Placebo-Controlled Trial. *J Clin Psychopharmacol*. 2017;37(2):155-161.[36]	Study population (adults) not identified in the CDR review protocol
Mier RJ, Bachrach SJ, Lakin RC, Barker T, Childs J, Moran M. Treatment of sialorrhea with glycopyrrolate: A double-blind, dose-ranging study. *Arch Pediatr Adolesc Med*. 2000;154(12):1214-1218.[16]	Comparator group (placebo) not identified in the CDR review protocol
Parr JR, Weldon E, Pennington L, et al. The drooling reduction intervention trial (DRI): a single blind trial comparing the efficacy of glycopyrronium and hyoscine on drooling in children with neurodisability. *Trials*. 2014;15:60.[37]	Protocol only (no data)
Parr JR, Todhunter E, Pennington L, et al. Drooling Reduction Intervention randomised trial (DRI): comparing the efficacy and acceptability of hyoscine patches and glycopyrronium liquid on drooling in children with neurodisability. *Arch Dis Child.* 2018;103(4):371-376.[4]	Dosing employed not identified in the CDR review protocol
Qurashi I, Chu S, Husain N, Drake RJ, Chaudhry I, Deakin JFW. Glycopyrrolate in comparison to hyoscine hydrobromide and placebo in the treatment of hypersalivation induced by clozapine (GOTHIC1): Study protocol for a randomised controlled feasibility study. *Trials*. 2016;17 (1) (no pagination)(553).[38]	Protocol only (no data)
Qurashi I, Chu S, Drake R, et al. Glycopyrrolate in comparison to hyoscine hydrobromide and placebo in the treatment of hypersalivation induced by clozapine (GOTHIC1): a feasibility study. Pilot feasibility study. 2019;5:79.[39]	Study population (adults) not identified in the CDR review protocol
Sridharan K, Sivaramakrishnan G. Pharmacological interventions for treating sialorrhea associated with neurological disorders: A mixed treatment network meta-analysis of randomized controlled trials. *J Clin Neurosci.* 2018;51:12-17.[40]	Study population (includes adults) not identified in the CDR review protocol

Reference	Reason for exclusion
Walshe M, Smith M, Pennington L. Interventions for drooling in children with cerebral palsy. *Cochrane Database Syst Rev*. 2012;11:CD008624.[5]	Systematic review formulation not identified in the CDR review protocol
Zeller RS, Davidson J, Lee HM, Cavanaugh PF. Safety and efficacy of glycopyrrolate oral solution for management of pathologic drooling in pediatric patients with cerebral palsy and other neurologic conditions. *Ther Clin Risk Manag*. 2012;8:25-32.[17]	No comparator
Colen-De Koning JCA, Man WH, Wilting I, et al. The effect of glycopyrronium bromide on nocturnal clozapine induced sialorrhoea in psychiatric patients. [German]. *Pharm Weekbl*. 2015;150(43):219-222.[41]	Comparator group (placebo) not identified in the CDR review protocol German publication
Anonymous. Glycopyrronium versus hyoscine for severe drooling. *Drug Ther Bull*. 2019;57(3):37.[42]	Study design (commentary) not identified in the CDR review protocol
Praharaj SK, Munoli RN, Sharma PS. Low-dose glycopyrrolate for clozapine-associated sialorrhea. *J Clin Psychopharmacol*. 2014;34(3):392.[43]	Study design (case report) not identified in the CDR review protocol
Pai S, Ghezzi EM, Ship JA. Development of a Visual Analogue Scale questionnaire for subjective assessment of salivary dysfunction. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2001;91(3):311-316.[44]	Study population (adults) not identified in the CDR review protocol

Appendix 3: Description and Appraisal of Outcome Measures

Aim

To describe the outcome measures outlined in Table 23 and review their measurement properties (validity, reliability, responsiveness to change, and minimal clinical important difference).

Findings

Table 23: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MCID
mTDS	9-point subjective scale categorizing severity and frequency of drooling	Validity: not identified Reliability: not identified	A change of 3 or more units from baseline is considered clinically meaningful as advised by the FDA.

MCID = minimal clinically important difference; mTDS = modified Teacher's Drooling Scale.

Modified Teacher's Drooling Scale

The mTDS is nine-point subjective scale used to measure drooling severity and frequency following saliva-control interventions and is based off of the Teacher's Drooling Scale.[45] The mTDS produces a score from 1 to 9 and scoring is as follows:[46]

1 = Dry: never drools

2 = Mild: only the lips are wet; occasionally

3 = Mild: only the lips are wet; frequently

4 = Moderate: wet on lips and chin; occasionally

5 = Moderate: wet on lips and chin; frequently

6 = Severe: drools to the extent that clothing becomes damp; occasionally

7 = Severe: drools to the extent that clothing becomes damp; frequently

8 = Profuse: clothing, hands, trays, and objects become wet; occasionally

9 = Profuse: clothing, hands, trays, and objects become wet; frequently

The mTDS is not a validated scale; although it has been used in clinical studies for the assessment of drooling.[16,17,31] According to the sponsor's submission for glycopyrrolate, the use of the mTDS is specifically recommended by the FDA Pediatric Advisory Subcommittee of the Antimicrobial Drugs Advisory Committee as an appropriate primary outcome variable for determining improvement in drooling.[46,47] A change of three units or more from baseline reflects the change from a minimum of one severity category (mild, moderate, severe, profuse) at a varying degree of frequency (frequent to occasional) and is considered clinically meaningful as advised by the FDA.[46,47] A MCID for mean change from baseline has not been identified in the literature.

References

1. Reddihough D, Erasmus CE, Johnson H, McKellar GM, Jongerius PH. Botulinum toxin assessment, intervention and aftercare for paediatric and adult drooling: international consensus statement. *Eur J Neurol.* 2010;17 Suppl 2:109-121.
2. Dias BLS, Fernandes AR, Maia Filho HdS. Sialorrhea in children with cerebral palsy. *J Pediatr (Rio J).* 2016;92(6):549-558.
3. Fox M. A guide to cerebral palsy. Toronto (ON): Ontario Federation for Cerebral Palsy; 2011: https://www.ofcp.ca/pdf/Web-Guide-To-CP.pdf. Accessed 2019 Sep 9.
4. Parr JR, Todhunter E, Pennington L, et al. Drooling Reduction Intervention randomised trial (DRI): comparing the efficacy and acceptability of hyoscine patches and glycopyrronium liquid on drooling in children with neurodisability. *Arch Dis Child.* 2018;103(4):371-376.
5. Walshe M, Smith M, Pennington L. Interventions for drooling in children with cerebral palsy. *Cochrane Database Syst Rev.* 2012;11:CD008624.
6. Clinical Study Report: FH-00-01. A double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of oral glycopyrrolate liquid (1 mg per 5 ml) for the management of problem drooling associated with cerebral palsy or other neurologic conditions in children [**CONFIDENTIAL** internal sponsor's report]. Atlanta (GA): Sciele Pharma, Inc; 2008 Jul 18.
7. Hockstein NG, Samadi DS, Gendron K, Handler SD. Sialorrhea: a management challenge. *Am Fam Physician.* 2004;69(11):2628-2634.
8. Lakraj AA, Moghimi N, Jabbari B. Sialorrhea: anatomy, pathophysiology and treatment with emphasis on the role of botulinum toxins. *Toxins (Basel).* 2013;5(5):1010-1031.
9. Reid SM, McCutcheon J, Reddihough DS, Johnson H. Prevalence and predictors of drooling in 7- to 14-year-old children with cerebral palsy: a population study. *Dev Med Child Neurol.* 2012;54(11):1032-1036.
10. Dohar JE. Sialorrhea & aspiration control - a minimally invasive strategy uncomplicated by anticholinergic drug tolerance or tachyphylaxis. *Int J Pediatr Otorhinolaryngol.* 2019;116:97-101.
11. Erasmus CE, Van Hulst K, Rotteveel JJ, Willemsen MAAP, Jongerius PH. Clinical practice: swallowing problems in cerebral palsy. *Eur J Pediatr.* 2012;171(3):409-414.
12. McCracken A. Drool control and tongue thrust therapy for the mentally retarded. *Am J Occup Ther.* 1978;32(2):79-85.
13. Tan EK, Lo YL, Seah A, Auchus AP. Recurrent jaw dislocation after botulinum toxin treatment for sialorrhoea in amyotrophic lateral sclerosis. *J Neurol Sci.* 2001;190(1-2):95-97.
14. Zeppetella G. Nebulized scopolamine in the management of oral dribbling: three case reports. *J Pain Symptom Manage.* 1999;17(4):293-295.
15. Heine RG, Catto-Smith AG, Reddihough DS. Effect of antireflux medication on salivary drooling in children with cerebral palsy. *Dev Med Child Neurol.* 1996;38(11):1030-1036.
16. Mier RJ, Bachrach SJ, Lakin RC, Barker T, Childs J, Moran M. Treatment of sialorrhea with glycopyrrolate: a double-blind, dose-ranging study. *Arch Pediatr Adolesc Med.* 2000;154(12):1214-1218.
17. Zeller RS, Davidson J, Lee HM, Cavanaugh PF. Safety and efficacy of glycopyrrolate oral solution for management of pathologic drooling in pediatric patients with cerebral palsy and other neurologic conditions. *Ther Clin Risk Manag.* 2012;8:25-32.
18. Senner JE, Logemann J, Zecker S, Gaebler-Spira D. Drooling, saliva production, and swallowing in cerebral palsy. *Dev Med Child Neurol.* 2004;46(12):801-806.
19. Reed J, Mans CK, Brietzke SE. Surgical management of drooling: a meta-analysis. *Arch Otolaryngol Head Neck Surg.* 2009;135(9):924-931.
20. Puraviappan P, Dass DB, Narayanan P. Efficacy of relocation of submandibular duct in cerebral palsy patients with drooling. *Asian J Surg.* 2007;30(3):209-215.
21. Andretta M, Tregnaghi A, Prosenikliev V, Staffieri A. Current opinions in sialolithiasis diagnosis and treatment. *Acta Otorhinolaryngol Ital.* 2005;25(3):145-149.
22. Burton MJ. The surgical management of drooling. *Dev Med Child Neurol.* 1991;33(12):1110-1116.
23. Glynn F, O'Dwyer TP. Does the addition of sublingual gland excision to submandibular duct relocation give better overall results in drooling control? *Clin Otolaryngol.* 2007;32(2):103-107.
24. Scully C, Limeres J, Gleeson M, Tomas I, Diz P. Drooling. *J Oral Pathol Med.* 2009;38(4):321-327.
25. Heywood RL, Cochrane LA, Hartley BE. Parotid duct ligation for treatment of drooling in children with neurological impairment. *J Laryngol Otol.* 2009;123(9):997-1001.
26. Cuvposa (glycopyrrolate): oral solution 1 mg/5 mL [product monograph]. Verdun (QC): Pediapharm Inc.; 2017 Oct 30.
27. Olsen AK, Sjogren P. Oral glycopyrrolate alleviates drooling in a patient with tongue cancer. *J Pain Symptom Manage.* 1999;18(4):300-302.
28. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol.* 2016;75:40-46.

29. Grey matters: a practical tool for searching health-related grey literature. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/grey-matters. Accessed 2019 Oct 23.

30. Zeller RS, Lee HM, Cavanaugh PF, Davidson J. Randomized phase III evaluation of the efficacy and safety of a novel glycopyrrolate oral solution for the management of chronic severe drooling in children with cerebral palsy or other neurologic conditions. *Ther Clin Risk Manag.* 2012;8:15-23.

31. Arbouw ME, Movig KL, Koopmann M, et al. Glycopyrrolate for sialorrhea in Parkinson disease: a randomized, double-blind, crossover trial. *Neurology.* 2010;74(15):1203-1207.

32. Ben-Pazi H. Drug treatment for children with cerebral palsy. *Harefuah.* 2006;145(7):510-515, 550.

33. Clinical Study Report: Sc-GLYCO-06-01. A six-month, multi-center, open-label study to assess the safety and efficacy of oral glycopyrrolate liquid for the treatment of pathologic (chronic moderate to severe) drooling in pediatric patients 3 to 18 years of age with cerebral palsy or other neurologic conditions [**CONFIDENTIAL** internal sponsor's report]. Atlanta (GA): Sciele Pharma, Inc; 2008 Aug 11.

34. Gronnebech H, Johansson G, Smedebol M, Valentin N. Glycopyrrolate vs. atropine during anaesthesia for laryngoscopy and bronchoscopy. *Acta Anaesthesiol Scand.* 1993;37(5):454-457.

35. Liang CS, Ho PS, Shen LJ, Lee WK, Yang FW, Chiang KT. Comparison of the efficacy and impact on cognition of glycopyrrolate and biperiden for clozapine-induced sialorrhea in schizophrenic patients: a randomized, double-blind, crossover study. *Schizophr Res.* 2010;119(1-3):138-144.

36. Man WH, Colen-de Koning JC, Schulte PF, et al. The effect of glycopyrrolate on nocturnal sialorrhea in patients using clozapine: a randomized, crossover, double-blind, placebo-controlled trial. *J Clin Psychopharmacol.* 2017;37(2):155-161.

37. Parr JR, Weldon E, Pennington L, et al. The Drooling Reduction Intervention trial (DRI): a single blind trial comparing the efficacy of glycopyrronium and hyoscine on drooling in children with neurodisability. *Trials.* 2014;15:60.

38. Qurashi I, Chu S, Husain N, Drake RJ, Chaudhry I, Deakin JF. Glycopyrrolate in comparison to hyoscine hydrobromide and placebo in the treatment of hypersalivation induced by clozapine (GOTHIC1): study protocol for a randomised controlled feasibility study. *Trials.* 2016;17(1):553.

39. Qurashi I, Chu S, Drake R, et al. Glycopyrrolate in comparison to hyoscine hydrobromide and placebo in the treatment of hypersalivation induced by clozapine (GOTHIC1): a feasibility study. *Pilot feasibility stud.* 2019;5:79.

40. Sridharan K, Sivaramakrishnan G. Pharmacological interventions for treating sialorrhea associated with neurological disorders: a mixed treatment network meta-analysis of randomized controlled trials. *J Clin Neurosci.* 2018;51:12-17.

41. Colen-De Koning JCA, Man WH, Wilting I, et al. The effect of glycopyrronium bromide on nocturnal clozapineinduced sialorrhoea in psychiatric patients. *Pharm Weekbl.* 2015;150(43):219-222.

42. Anonymous. Glycopyrronium versus hyoscine for severe drooling. *Drug Ther Bull.* 2019;57(3):37.

43. Praharaj SK, Munoli RN, Sharma PS. Low-dose glycopyrrolate for clozapine-associated sialorrhea. *J Clin Psychopharmacol.* 2014;34(3):392.

44. Pai S, Ghezzi EM, Ship JA. Development of a Visual Analogue Scale questionnaire for subjective assessment of salivary dysfunction. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2001;91(3):311-316.

45. Camp-Bruno JA, Winsberg BG, Green-Parsons AR, Abrams JP. Efficacy of benztropine therapy for drooling. *Dev Med Child Neurol.* 1989;31(3):309-319.

46. CDR submission: Cuvposa (glycopyrrolate), oral solution 1 mg/5 mL [**CONFIDENTIAL** sponsor's submission]. Verdun (QC): MEDEXUS Pharmaceuticals, Inc.; 2019 May 23.

47. Center for Drug Evaluation Research. Medical review(s). *Cuvposa (glycopyrrolate), oral solution. Company: Shionogi Pharma, Inc. Application No.:022571. Approval date: 07/28/2010 (FDA approval package)*. Rockville (MD): U. S. Food and Drug Administration (FDA); 2010: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022571Orig1s000MedR.pdf. Accessed 2019 Oct 24.