DUS Title	Drug Utilization Study on the Risk Minimisation Tools for Sialanar
Proveca Protocol No.	PRO/GLY/004
Date/version Protocol	21 MAR 18 V5.0
PASS	No, drug utilisation/observational study
EU PASS register No.	N/A
Active substance	Glycopyrronium bromide
Medicinal product	Sialanar
Product reference	
Research question and objectives	The purpose of this drug utilisation study is to establish whether or not the HealthCare Educational Material and Reminder card for Caregivers [together the 'educational materials'] that have been put in place for Sialanar have been followed and are effective. Primary Objective • The primary objective is to monitor and assess effectiveness of the educational materials helping carers to adjust dose titration in response to identified anticholinergic side effects Endpoint: Incidence of anticholinergic side effects resulting in treatment dose change or cessation of Sialanar. Secondary Objectives • The number of anticholinergic adverse events brought to the attention of the prescribing physician (initiator – e.g. consultant neurologist) by the carer that occurs in between the routine consultation time interval. • The number of occasions and reasons Sialanar treatment is stopped due to anticholinergic adverse events. • Quantify the frequency of off-label use of Sialanar.
Countries of study:	UK and at least 4 additional EU countries depending on launch dates and plans.
Marketing Authorisation Holder (MAH)	Proveca Ltd, Neo, Charlotte Street, Manchester, M1 4ET
MAH contact	Dr Helen Shaw (MB, ChB, Dip Pharm Med), Director, Proveca Ltd

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Adverse event reporting	Adverse events will be documented from visit 1. Events experienced before that time will be regarded as part of the medical history of the subject.
AE	Adverse event
DMP	Data management plan
EMA	European Medicines Agency
Enrolled patient	Patient allocated a patient number which confirms formal entry into the study
EU	European Union
GCP	Good Clinical Practice
HRA	Healthcare Research Authority
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
N	Number of subjects
PRAC	Pharmacovigilance Review Advisory Committee
Recruiting Physician	The physician recruiting patients with chronic sialorrhoea into the study.
SAE	Serious adverse event
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
Withdrawal	Enrolled subject who was withdrawn by the investigator before completion of the observational phase of the study

3. RESPONSIBLE PARTIES

The following individuals are authors of this protocol:

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4. ABSTRACT

Title: Drug Utilisation Study on the Risk Minimisation Tools for Sialanar

Rationale and background:

Proveca have recently been granted a Paediatric Use Marketing Authorisation (PUMA) (15th September 2016) for Sialanar® for the symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders. Proveca will conduct a DUS to monitor and assess the effectiveness of additional risk minimisation measures for anticholinergic side effects that may be dose dependent.

This DUS will use a real life observational approach for assessing the risk minimisation measures in place, i.e. the product information provided to healthcare professionals (SmPC, PIL and Healthcare Educational Material) and for the patient's carer (PIL and Reminder card for Caregiver), which specifies how side effects should be managed while patients are being treated with Sialanar®.

Research question and objectives:

The purpose of this drug utilisation study is to establish whether or not the risk minimisation measures, HealthCare Educational Information and Reminder Card for Care-giver that have been put in place for Sialanar have been followed and are effective.

Primary Objective

- The primary objective is to monitor and assess effectiveness of the educational material helping carers to adjust dose titration in response to identified anticholinergic side effects

Endpoint:

Incidence of anticholinergic side effects resulting in treatment dose change or cessation of Sialanar.

Secondary Objectives

- The number of anticholinergic adverse events brought to the attention of the prescribing physician (initiator – e.g. consultant neurologist) by the carer that occur in between the routine consultation time interval.
- The number of occasions Sialanar treatment is stopped due to anticholinergic adverse events, by type.
- Quantify the frequency of off-label use of Sialanar.

Study design:

Non-interventional, multi-centre /multi-country (UK to commence first), observational study. Specialist physicians who for this study are referred to as recruiting physicians (as they are responsible for the information recorded into the study database), examples of the types of physicians are: Paediatric Neurologists and Community Paediatricians who prescribe Sialanar for the treatment of sialorrhoea. The recruiting physicians will ask the patient's carer if they are

willing to participate; patients will include those who have previously used glycopyrronium bromide specials formulation, those new to Sialanar or have been exposed to Sialanar for the period between launch and joining the study. The recruiting physician will provide and explain information on Sialanar, the pack insert label and Reminder Card for Carer-givers (educational material for care-giver, see Annex 1). The recruiting physician will enter baseline data regarding the patient's underlying diagnosis relating to sialorrhoea, the drooling status and other variables such as age, weight, dose of Sialanar. At follow up visits drooling status, dosing changes/dose interruptions and any adverse events will be recorded. At the final visit, in addition to what is recorded in the follow up visits, the recruiting physician will also record how useful they have found the risk minimisation information and also care-givers opinion of usefulness/understanding of the educational material (via VAS within the study database). All data will be entered directly into a study database by the recruiting physician at the start of the study (initial visit) and at each visit (follow-up visits) that the patient attends for a period of 12 months.

Population:

Approximately 10 to 30 specialist centres that treat chronic sialorrhoea will be included per country; the plan will be to recruit a minimum of 100 patients per country. The participants will be representative of the physicians who are prescribing Sialanar in each of the countries. Ideally 12 months data is required per patient but descriptive analysis will occur for those that have both the initial (baseline) and at least one follow up visit completed.

Variables:

Information will be recorded about the patient e.g. demographics, medical history relating to the diagnosis of sialorrhoea. In addition the following will be recorded for the prescription at each visit during the 12 month period:-

- Drooling status according to the modified Teacher's Drooling Scale (mTDS)
- Dose prescribed and any up or down titrations that occur between visits or adjusted at the visit
- Stopping treatment – temporary or permanent
- Adverse events
- Physician and carers' opinion of the educational material (according to 11 point VAS scale).

Data sources:

A study portal database has been developed specifically for this study and data will be entered directly into the database by the treating physician.

Study size:

There is no sample size calculation as there is no hypothesis testing. A minimum of 100 patients will be recruited in each of the five countries.

Data analysis:

Descriptive statistics will be used. The analysis will be performed per country if possible and for all countries combined (if possible for same data categories). Demographic characteristics and Sialanar treatment outcomes will be summarised according to diagnosis (if possible and sufficient numbers).

Milestones:

Registration of the potential recruiting physicians began in February 2017, the protocol was submitted for Research Ethics Committee Review July 2017 and a change in Principal Investigator was made in January 2018. It is expected that recruitment of patients will begin in April 2018; the study is planned to complete (after five countries have participated) in December 2022.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Submission to EC/HRA (UK)	July 2017
Start of data collection (first country)	April 2018
Submission to IEC/IRB (2nd country onwards)	May 2018
End of data collection (last country)	December 2022
Final report of study results	June 2023

7. RATIONALE AND BACKGROUND

Proveca have recently been granted a Paediatric Use Marketing Authorisation (PUMA) (15th September 2016) for Sialanar® for the symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders. Proveca agreed to conduct a DUS to monitor and assess the effectiveness of additional risk minimisation measures for anticholinergic side effects that may be dose dependent.

Drooling is characterised by the loss of saliva from the mouth. Severity of sialorrhoea ranges widely, from mild droolers who spill saliva onto their lips but not beyond the vermillion border, to severe droolers whose saliva spills onto their clothes and immediate environment. A child will

typically produce 1-1.5 litres of saliva per day. In children with cerebral palsy, drooling may stem from difficulties in swallowing rather than production of excess saliva (Senner et al 2004).

There is no standard treatment of sialorrhoea. First-line management of sialorrhoea (chronic pathological drooling) should be directed at the cause, which may be multifactorial and patient-specific (Brodtkorb et al 1988). Several options are available including practical aids, speech therapy, physiotherapy, surgery and medication. Each option has varying degrees of acceptability and success (Zeppetella 1999) and optimisation of quality of life without compromising overall health must be paramount when choosing appropriate treatment (Fairhurst and Cockerill 2010). A survey conducted by Proveca to assess how sialorrhoea is treated in the EU demonstrates that there is no uniform approach to treatment (Proveca Report 2012).

Until recently, no drugs were approved for the treatment of excessive drooling in EU. Anticholinergic drugs approved for other indications are used as off-label treatment for excessive drooling in children with cerebral palsy.

This DUS will use a real life observational approach for testing the value of the risk minimisation measures in place, i.e. the product information provided to healthcare professionals (SmPC, PIL and Healthcare Educational Material) and for the patient's carer (PIL and Reminder card for Caregiver), which specify how side effects are managed while patients are being treated with Sialanar®.

8. RESEARCH QUESTION AND OBJECTIVES

The purpose of this drug utilisation study is to establish whether or not the risk minimisation measures, HealthCare Educational Information and Reminder Card for Caregiver that have been put in place for Sialanar have been followed and are effective.

8.1. Primary Objective

The primary objective is to monitor and assess effectiveness of the educational materials helping carers to adjust dose titration in response to identified side effects.
Endpoint:
Incidence of anticholinergic side effects resulting in treatment dose change or cessation of Sialanar.

8.2. Secondary Objectives

The secondary objectives are:

- The number of adverse events (number of anticholinergic adverse events will be separated) brought to the attention of the prescribing physician (initiator – e.g. consultant neurologist) by the carer that occur in between the routine consultation time interval.
- The number of occasions and reasons Sialanar treatment is stopped due to anticholinergic adverse events.

- Quantify the frequency of off-label use of Sialanar

9. RESEARCH METHODS

9.1. Study design

It is planned that this study will commence firstly in the UK approximately six months post launch of Sialanar® on the UK market. The plan is to conduct the study in at least five European countries (UK first) involving 10 to 30 centres in each country; each country recruiting a minimum of 100 patients. Specialist physicians will be invited to register their interest in participating in the study via the Proveca Sialanar DUS Web Database during the pre-study approval phase in their country. Each registration will be reviewed and verified by the Proveca Medical Director, and a confirmation of success or failure of their application will be sent to each physician.

The treating physician will ask any patients/patient's carers if they are willing to participate; patients will include those who have used glycopyrronium bromide specials formulations, those new to Sialanar or those exposed to Sialanar for the period between launch and joining the study. The study will be explained, along with the risk minimisation documents, and what data will be collected and how it is captured within the study database. It will also be explained that they have the right to withdraw at any time during the study and their medical care will not be prejudiced. Once the patient/patient's carer have had time to consider the study and the opportunity to ask questions, if they are interested in the study, they will sign an informed consent form to indicate their consent in participating in the study. The informed consent form must be signed by the patient/patient's carer and the treating physician. The consent form will be retained at the recruiting physician's site, for 100% remote monitoring of informed consent purposes a copy will be scanned to the study database (where local regulations allow) and a copy of the consent form and study information sheet will be provided to the patient/patient carer.

9.2. Setting

The patients will attend their usual clinic for their medical appointment review, there is to be no change due to the involvement in this study. The setting will vary across the European countries depending on the medical set up/infrastructure within each country; for example, hospital based appointment, non-hospital community-based treatment centres or general practitioners.

The accessible patient study population will be that portion of the target population with chronic drooling where participating prescribing physicians treat or intend to treat with Sialanar in the clinical practice setting. Paediatric neurologists and community paediatricians planning to prescribe Sialanar for their patients for the treatment of chronic drooling due to neurological conditions will be eligible for involvement in this DUS if they have received Good Clinical Practice training (according local regulations).

This is an observational study, the intention of the study is to not be prescriptive on how the physicians should prescribe and manage Sialanar but to assess the risk minimisation measures that are in place for Sialanar and assess their value in helping carers manage dose dependent anticholinergic adverse effects through dose adjustment after starting treatment. Patients will attend for an initial visit and ideally they will remain in the study for 12 months. During the 12 months it is anticipated that the patient will attend for 4 further visits; approximately every 3 months recommended in the SPC for Sialanar. The physician will record a number of measurements related to the patient's disease type, severity of drooling, treatment titrations, any withdrawals from treatment (temporary and permanent), adverse events and opinion of the educational material.

9.2.1. Inclusion criteria

Patients who have consented to the study and are prescribed Sialanar at the time of entry into the study.

9.2.2. Exclusion Criteria

This is a DUS assessing the effectiveness of the educational material accompanying the prescribing of Sialanar, and follows normal clinical practice, therefore no exclusion criteria has been applied.

9.2.3. Study Visits

Initial Visit

Informed consent as per 9.1; then the recruiting physician will record: the patients' demographics (month/year of birth, gender and weight), and confirmation of diagnosis. They will record the patient's drooling status, co-morbidities and concomitant medication; all data will be entered on the eCRF.

The initial prescribed dose will also be recorded. The recruiting physician will explain all educational material to the carer and copies will be provided.

Visits 2-4 and Final Visit

At the interim visits (expected to be between two and four visits during the 12 months as per the usual practice for the diagnosed condition), the physician will record the following information on the study database:

Reason for the visit: Routine follow-up; follow-up initiated by the carer; other

Adverse events;

Dosage: whether continuing on existing dose; dose change and reason; temporary or permanent discontinuation of dose.

Drooling status: mild; moderate; severe.

The action the Carer has taken with regard to educational material and any required dose titrations

Withdrawal: if the patient withdraws from the study, this will be recorded in the database, if possible a record of whether the patient is discontinuing Sialanar and the VAS will be completed; no further information will be recorded (occurs prior to 12 month visit)

At the final visit, in addition to what is recorded in the follow up visits, the recruiting physician will also record how useful they have found the educational material and also the care-givers opinion of usefulness/understanding of the educational material (both measurements via 11 point 0 to 10 VAS entered into the study database).

Healthcare Educational Material - *Physician's opinion*	0 – Not useful	10 – Very useful
Reminder Card for Caregiver - *Physician's opinion*	0 – Not useful	10 – Very useful
Reminder Card for Caregiver - *Caregiver's opinion*	0 – Did not understand	10 – Understood well

Completed: In addition to recording usual visit information, the date completed will be recorded and whether patient continues with Sialanar post study. 12 months observation period: record of whether patient discontinues Sialanar/discontinues or completes 12 month observation period.

The study duration is approximately 12 months for each patient.

The estimated date of first patient enrolled is April 2018 and the estimated date of last patient completed in the study is December 2022. The study will be initiated in a minimum of 5 European countries within 6 month of the launch of Sialanar.

9.3. Variables

Information will be recorded about the patient e.g. demographics, medical history relative to the diagnosis of sialorrhoea. In addition the following will be recorded about the prescription at each visit during the 12 month period:-

- Drooling status according to the drooling impact scale
- Dose prescribed and any up or down titrations that occur between visits or adjusted at the visit
- Stopping treatment – temporary or permanent
- Anticholinergic and all adverse events
- Physician and carers' opinion of the educational material (according to 11 point scale).

Any off label prescribing will be recorded, see Table 1, they will be recorded in the study database as pre-existing conditions.

Table 1: Contraindications & precautions

Contraindications:	
Hypersensitivity to the active substance or to any of the excipients	
Pregnancy and breast-feeding.	
Glaucoma.	
Myasthenia gravis	
Renal conditions:	Urinary retention; Severe renal impairment (eGFR <30 ml/min/1.73m^2), including those with end-stage renal disease requiring dialysis; Mild to moderate renal impairment
GI conditions:	History of intestinal obstruction, ulcerative colitis, paralytic ileus, pyloric stenosis.
Concomitant treatment with	*potassium chloride solid oral dose; anticholinergics;*
Precautions:	
Mild to moderate sialorrhoea	Sialanar should not be given to children with mild to moderate sialorrhoea.
Cardiac disorders	Acute myocardial infarction; Hypertension; Coronary artery disease; Cardiac arrhythmias and conditions characterised by tachycardia.
Gastro-Intestinal disorders	Gastro-oesophageal reflux disease, pre-existing constipation and diarrhoea.
CNS adverse events	Caution should be exercised in children with compromised blood brain barrier eg. Intraventricular shunt, brain tumour, encephalitis.
Children below the age of 3years	Sialanar is not recommended in children below the age of 3 years since there is very limited data on the efficacy and safety of glycopyrronium in this age group.

9.4. Data Sources

Information will be entered directly into the study database at the time of the patient's visit or immediately afterwards. In accordance with data privacy regulations personal data will be logged on a separate sheet (paper) and filed within the physician's premises; the electronic version of personal data will be stored separately on the study web portal and will include the patient's initials and month/year of birth only.

Periodic review and manual checks of the data entered into the study web portal (patients identified only as patient ID No., initials and physician's location) will occur in order to review for completeness; any missing data/ambiguities will be clarified directly with the physician.

9.5. Study Size

There is no sample size calculation as there is no hypothesis testing. A minimum of 100 patients will be recruited in each of the countries.

9.6. Data Management

9.6.1. Databases

Study data will be entered into the study web database at the recruiting physician's site, saved to a central data base and all changes will be tracked in order to provide an audit trail. Proveca personnel will be able to identify a patient by their unique patient ID only; no personal identifiers will be provided to or stored by the Sponsor (Proveca). In order to ensure study data security and confidentiality, strict access controls will be applied – individual access/log on with different write/view access for different roles, access will be provided to authorised personnel only.

The prescribing physician (or delegate) will record any patient-identifying information securely in a supplied file which will provide a match to the patient ID data in the database.

9.6.2. Dataflow

Data is entered at the time of the visit or soon after by the prescribing physician or a delegate within their team. Study data is checked remotely by a Proveca representative on an ongoing basis throughout the study so that immediate follow-up of any missing or incorrect data can be queried and entered. Any missing data will be evaluated and described. Due to the nature of this study, no imputation of missing data is planned.

9.6.3. Database Freeze/Lock

Once a patient has completed 12 months, data will be checked, deemed "clean" and the data will be locked to prevent any further editing. The database will be locked at country level within four weeks of the last the patient to complete 12 months.

10. PROTECTION OF HUMAN SUBJECTS

This drug utilisation study will be conducted in accordance with the protocol and applicable national and European regulatory requirements and laws. Specifically the rights, privacy and well-being of patients will be observed by following the ethical principles that have their origin in the Declaration of Helsinki, International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and, additionally the ENCePP code of conduct [EMA/929209/2011, May 2010] will be observed.

10.1. Ethics Committees/Institutional Review

The protocol will be reviewed by ethics committees/institutional review boards as applicable for each geographical location.

10.2. Informed Consent

The recruiting physician will explain the purpose and describe the non-interventional nature of the study to the patient carer/patient. A written explanation of the study will be provided in the form of a patient information sheet (PIS); the physician will obtain written informed consent from the patient carer/patient by their signing of the Informed Consent Form (ICF). A copy of the PIS and ICF will be provided to the patient carer/patient and a copy of each document filed within study file in the physician's department.

Patients will have the right to withdraw their consent at any time during the study.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

This is an observational study, it is non-interventional; in line with the updated Guideline of Good Pharmacovigilance Practices(GVP) (Module VIII) dated 09 October 2017 all adverse events will be recorded from the time the patient enters in to the study until the final/completion visit.

Adverse events (observed or volunteered) will be recorded on the eCRF via the web study database. Serious Adverse Events must be recorded onto the eCRF within 24 hours of the investigator site becoming aware of the SAE.

An automatic email is sent from the study web database to the Sponsor when an adverse event is entered on to the AE or SAE eCRF.

All suspected adverse reactions are subject to expedited reporting to the European Medicines Agency (EMA). Expedited reporting will be performed by the Sponsor's pharmacovigilance provider. Serious ADRs will be submitted to the EMA no later than 15 days from the date of initial receipt. Non serious ADRs will be submitted to the EMA no later than 90 days from initial receipt.

Follow up of AEs and SAEs will continue until resolution or no further change.

11.1. Adverse Events

<u>Adverse event</u>

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

<u>Serious adverse event</u>

A serious adverse event is defined as any AE which

- results in death,

- is life-threatening,

- requires in-patient hospitalization, or prolongation of existing hospitalisation,

- results in persistent or significant disability or incapacity, or - is a congenital anomaly/birth defect

- other serious event: medical and scientific judgement should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Start-up report including cohort accrual estimate, ethics approval plan etc (July 2017)

12 month progress report including recruitment progress (July 2018)

Annual report per country. Data lock every 12 months after study start report 3 months later

Final report. Data lock 3 months after last patient completed (TBC July 2022), report 4 months later (TBC Nov 2022) in PSUR and as study report.

13. REFERENCES

Brodtkorb E, Wyzocka-Bakowska MM, Lillevold PE et al. Transdermal scopolamine in drooling. Journal of Mental Deficiency Research 1988; 32: 233-237

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Fairhurst CBR, Cockerill H. Management of drooling in children. Arch Dis Child Educ Pract Ed. 2011; 96: 25-30.

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Senner JE, Logemann J, Zecker S, Gaebler-Spira D. Drooling, saliva production and swallowing in cerebral palsy. Dev Med Child Neurol 2004; 46: 801-6.

Zeppetella 1999 Zeppetella G. Nebulized scopolamine in the management of oral dribbling: three case reports. J Pain Symptom Manage 1999;17:293-295

APPENDIX 1 LIST OF STAND ALONE DOCUMENTS

Summary of Product Characteristics
Patient Information Leaflet
Healthcare Educational Information
Reminder Card for Caregiver
Patient Information Sheet and Informed Consent Form (PIS, ICF)