Title	The Performance and Safety of Petit Drill in the French Paediatric Population: a post-market clinical follow-up.
CIP Version and Date	V6.0 26 March 2024
Revision history	*Summary of the revision history in the case of amendments* *Amendment 2* *Sponsor information section: Dr Bernard SIMIAN added as new investigator.* *Amendment 1* *Section 1 (Number of patients required and enrolment duration) section 6.6, section 6.9.7 and section 7.13: number of participating pharmacies updated from 100 to around 125.* *Section 7.13: pre-screening period updated from "June" to "July" to stick to the 9 month period length and mean of number of patients per pharmacy modified from "2 à 3" to "2".* *Section 14.2 and section 14.3: wording of "investigating pharmacist" modified as follow: "investigator".*

SPONSOR INFORMATION

Sponsor	Pierre Fabre Médicament. Les Cauquillous, 81500 LAVAUR, FRANCE.
Investigator(s)	Dr Myriam SIMIAN (Coordinating Investigator) Dr Carole PERRIN Dr Sébastien BUCQUET Dr Rémi ROCHELET Dr Esther MILOJEVITCH Dr Bernard SIMIAN The different roles, responsibilities and qualifications of investigators are specified in the Investigator list.
Investigation site(s)	CEN EXPERIMENTAL (Clinical Investigation Centre) 18, rue Pauline Kergomard 21000 DIJON, France *Note: The sponsor shall maintain an updated list of principal investigators, investigation sites, and institutions. This list can be kept separately from the CIP. The definitive list shall be provided with the clinical investigation report.*
Other organisations	CEN (CRO) 18, rue Pauline Kergomard 21000 DIJON, France
Coordinating Pharmacist & scientific committee	**Coordinating Pharmacist** Dr Vincent ALQUIER **Scientific committee** Dr Vincent ALQUIER Pr Guy DUTAU (Pediatrician pulmonologist)

TABLE OF CONTENTS

Sponsor Information 2
Table of contents 3
List of Tables 7
List of abbreviations 8
1 Synopsis of the clinical investigation 10
2 Identification and Description of the Investigational Device 17
2.1 Summary Description of the investigational device 17
2.2 Manufacturer of the Investigational Device 17
2.3 Model/type of the Investigational Device 17
2.4 Traceability 17
2.5 Intended Purpose 18
2.6 Populations and Indications 18
2.7 Clinical, Technical and Biological Description of the Investigational Device 18
2.8 Training requirements 19
2.9 Special Medical Procedures 19
2.10 Instructions for Use 19
3 Justification for the design of the clinical investigation 20
3.1 Background and Rationale 20
3.1.1 Risks associated with existing cough relief treatments 20
3.1.2 Glycerol as an effective and safe alternative for dry cough management 21
3.1.3 Rationale 21
3.2 Evaluation of relevant pre-clinical assessment 21
3.3 Evaluation of relevant clinical data 22
3.3.1 Description of the pathology 22
3.3.2 Data issued from clinical published studies on similar devices 22
3.3.3 Data issued from clinical investigations on the device 22
3.3.4 Safety data recorded from vigilance records 24
3.4 Clinical development stage 24
4 Risks and benefits of the investigational device and clinical investigation 25
4.1 Anticipated clinical benefits 25
4.2 Anticipated adverse device effects 25
4.3 Risks associated with participation in the clinical investigation 25
4.4 Possible interactions with concomitant medical treatments 25
4.5 Actions to control or mitigate risks 25
4.6 Risk-to-benefit rationale 25

5 Objectives and hypotheses of the clinical investigation ____ 27

5.1 Objectives ____ 27
5.1.1 Primary objective ____ 27
5.1.2 Secondary objectives ____ 27
5.1.3 Exploratory objectives ____ 27

5.2 Hypotheses (if applicable) ____ 27

5.3 Risks and anticipated adverse device effects to be assessed ____ 27

6 Clinical Investigation Design ____ 28

6.1 Type of clinical investigation ____ 28

6.2 Bias minimization ____ 28

6.3 Outcomes ____ 29
6.3.1 Primary outcome ____ 29
6.3.2 Secondary outcome(s) ____ 29
6.3.3 Exploratory outcomes ____ 30

6.4 Variables ____ 31

6.5 Replacement of subjects ____ 38

6.6 Investigation sites ____ 38

6.7 Clinical investigation end ____ 38

6.8 Investigational device(s) and comparators ____ 38
6.8.1 Exposure ____ 38
6.8.2 Justification of the choice of comparator ____ 38
6.8.3 Other needed medical device or medication ____ 38
6.8.4 Number of investigational devices to be used ____ 38

6.9 Subjects ____ 38
6.9.1 Inclusion criteria ____ 39
6.9.2 Exclusion criteria ____ 39
6.9.3 Subject withdrawal and lost-to-follow-up ____ 39
6.9.4 Expected duration of the clinical investigation ____ 40
6.9.5 Expected duration of each subject's participation ____ 40
6.9.6 Sample size ____ 40
6.9.7 Period and point of enrolment ____ 40
6.9.8 The investigation population relative to the target population ____ 40
6.9.9 Vulnerable populations ____ 41

6.10 Procedures ____ 41

6.11 Monitoring plan ____ 42

7 Statistical considerations ____ 43

7.1 Analysis population ____ 43

7.2 Statistical Design and Analytical Methods ____ 43

7.3 Level of significance and power ____ 43

7.4 Determination of Sample Size ____ 43

7.5 Pass/fail criteria ____ 44

7.6 Interim analyses 44
7.7 Criteria for the termination of the clinical investigation (if applicable) 44
7.8 Management of biases 44
7.9 Deviations from the original statistical analysis plan 44
7.10 Subgroups 44
7.11 Handling of missing data and drop-outs 44
7.12 Exploratory analyses 44
7.13 Number of subjects in each pre-screening centre 45
8 Data Management 46
8.1 Data recording 46
8.1.1 Case Report Forms 46
8.1.2 Mobile application 46
8.1.3 Specification of source documents 46
8.2 Data Management System 46
8.2.1 Procedures for data review, database cleaning and data queries. 46
8.2.2 Procedures for data entry, verification, validation 47
8.2.3 Database locking and storage 47
8.2.4 Confidentiality and data protection 47
8.2.5 Procedures for data retention 47
9 Amendments to the clinical investigation plan 48
10 Deviations from the clinical investigation plan 48
11 Device accountability 48
12 Statements of compliance 49
12.1 General statements of compliance 49
12.2 Ethics and Regulatory Authority approval 49
12.3 Financing 50
13 Informed consent process 51
14 Management and reporting of Adverse events, adverse device effects and device deficiencies 53
14.1 Definitions 53
14.1.1 Adverse Event (AE) - Article 2 (57) from MDR 53
14.1.2 Serious Adverse Events (SAE) - Article 2 (58) from MDR 53
14.1.3 Device deficiencies (DD) - Article 2 (59) 53
14.1.4 Incident – Article 2 (64) 54
14.1.5 Serious incident – Article 2 (65) 54
14.2 Assessment of AE and SAEs 54
14.3 Reporting of medical device cases 55
14.4 Sponsor’s responsibilities for safety reporting purposes 56
15 Vulnerable population 56
16 Suspension or premature termination of the clinical investigation 57
16.1 Definitions 57

16.2 Criteria for suspension or early termination 57
17 Publication policy 58
18 Annex 59
18.1 ANNEX I: IFU 59
18.2 ANNEX II: DT-034-PFM-520-01 Product risk management 59
18.3 ANNEX III: PCQ 59
18.4 ANNEX IV: PAC-QoL 60
18.5 ANNEX V: VAS 62
19 Bibliography 63
19.1 Guides and standards for the preparation of the CIP 64
Signature page 65

LIST OF TABLES

Table 1: Composition of the Petit Drill Syrup 18
Table 2: Variables to be collected at patient enrolment 31
Table 3: Variables to be collected during patient follow-up by the parent/legal representative 34
Table 4: Variables to be collected by the investigator in case of AE or DD occurring during patient follow-up 36

LIST OF ABBREVIATIONS

ADE	Adverse Device Event
AE	Adverse Event
ANSM	*Agence Nationale de sécurité du médicament et des produits de santé*
CI	Confidence Interval
CIR	Clinical Investigation Report
CIP	Clinical Investigation Plan
CPP	Comité de Protection des Personnes
CRO	Clinical Research Organization
CSS	Cough Symptom Score
CSQ-8	Client Satisfaction Questionnaire
D0	The day before treatment initiation
D1	The first day of treatment initiation
D2	The second day of treatment initiation
D3	Third day of treatment
DD	Device Deficiencies
EC	Ethics Committee
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
IMDRF	International Medical Device Regulators Forum
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HCP	Healthcare Professional
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IFU	Instructions for Use
K-LCQ	Korean version of Leicester Cough Questionnaire
MCID	Minimum Clinically Important Difference
MD	Medical Device
MDCG	Medical Device Coordination Group guidelines
MDD	Medical Device Directive
MDR	Medical Device Regulation
MHRA	Medicines and Healthcare products Regulatory Agency
NBOG	Notified Body Operations Group
NRS	Numeric Rating scale
OTC	Over-the-Counter
PAC-QoL	Parent-proxy Children's Acute Cough-specific QoL Questionnaire

PCQ	Pediatric Cough Questionnaire
PMCF	Post-Market Clinical Follow-up
PRO	Patient Reported Outcome
QoL	Quality of Life
QC	Quality Control
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SD	Standard Deviation
URTI	Upper Respiratory Tract Infection
VAS	Visual Analogue Scale
WHO	World Health Organisation

1 SYNOPSIS OF THE CLINICAL INVESTIGATION

Clinical investigation title	The Performance and Safety of Petit Drill in the French Paediatric Population: a post-market clinical follow-up study.
Sponsor	Pierre Fabre Médicament Les Cauquillous, 81500 LAVAUR, FRANCE.
Device description (name, model, etc.)	Petit Drill: Glycerol Syrup Oropharyngeal Mucosa Protection Material PR2506. Class IIa medical device (MD) following Rule 5 and Rule 21 of Appendix VIII of the new medical device regulation (EU) 2017/745 (MDR). The device belongs to the category MDN 1213 “Non-active, non-implantable medical devices composed of substances to be introduced into the human body via a body orifice or the dermal route”. Petit Drill is a clear and colorless syrup consisting of glycerol (0.75 mL/5 mL or 15% v/v), with a strawberry flavor presented in a 125 mL amber glass bottle of type III (Eur. Pharm. 3.2.1). The syrup is for oral use and to be applied with a measuring pipette. The 5 mL measuring pipette is included for dosing the oral situation. The pipette is a class I device with measuring function according to medical device directive 93/42/EEC. The measurement function of the pipette has been validated by Rovipharm for 60 uses (DT-034-PFM-324).
Intended purpose	The intended use is the treatment of throat irritation (sore throat) associated with dry cough for infants starting at 6 months of age and in children up to 6 years of age.
Comparator(s)description, if applicable	Not applicable.
Clinical development stage	Post-Market Clinical Follow-up.
Design of the clinical investigation	National (French), single-arm prospective, observational, longitudinal clinical investigation.
Rationale	Demulcent / Soothing substance is the currently recommended option to alleviate throat irritation associated to cough and sore throat in children under 6 years. The intended benefit to the patient of Petit Drill is to calm throat irritation (sore throat) associated to dry cough in infants starting at 6 months of age and in children up to 6 years of age. This intended benefit sustained by the properties of the formula is recognized and promoted by the World Health Organization, health authorities and current textbooks to have a positive impact on patient management for the targeted population (infant / child). Pierre Fabre Médicament wishes to generate its own clinical data of this product in a real-life context, in order to support the clinical evaluation. Performance and the safety of Petit Drill will be assessed in children presenting throat irritation to support the conclusion of clinical evaluation report.

Objectives	**Primary Objective:** To assess the performance of the Petit Drill medical device in the treatment of throat irritation (sore throat) associated with dry cough in infants starting at 6 months of age and in children up to 6 years of age. **Secondary Objectives:** • SO1. To describe the clinical and sociodemographic characteristics of children using Petit Drill. The following secondary objectives will describe the performance and clinical benefit of Petit Drill in terms of: • SO2. Changes in nightly cough frequency, severity, bothersome for the child, and ability to sleep for child and parent(s) throughout the 3 day-treatment; • SO3. Changes in daily cough severity; • SO4. Evolution of Quality of life. The following secondary objectives will describe the use and safety of Petit Drill: • SO5. Adherence to use of Petit Drill Syrup; • SO6. Parents' satisfaction with Petit Drill use; • SO7. Safety of the Petit Drill medical device in infants aged from 6 months to children up to 6 years of age. **Exploratory Objectives:** • SO8. To describe the dispensing modalities of Petit Drill by age group; • SO9. To describe the study objectives (except SO8) according to child's range of age.
Duration of the clinical investigation	Duration of the inclusion period: 9 months. Maximal duration of follow-up for a patient: 4 days. Overall study duration: 9 months.
Number of Patients required and enrolment duration	**Determination of Sample Size:** A total of 196 patients would provide the necessary precision of 7% of the confidence intervals (CI) for primary outcome in the most statistically unfavorable scenario (performance outcome of 50%), given that currently available publications cannot allow for an accurate estimate of the expected primary outcome for one device. In a previous observational study, a drop-out rate of 27% was observed in a cohort of children from 1 to 3 years of age, with a longer follow-up period and uncertainty regarding the mode of administration of patient questionnaires, which may suggest a slight overestimation compared to the proposed clinical investigation. Based on this result, a 20% drop-out is anticipated.

	Number of patients to enrol: 245 patients (considering a 20% dropout rate). **Enrolment duration:** approximately 6 to 9 months (at least from November 2023). • Considering around 125 sites throughout France will be recruited and a 25% participation acceptance rate (optimal scenario) upon proposal of the clinical investigation, a maximum accrual period of 6 to 9 months should allow to reach the target sample size.
Eligibility Criteria	**Inclusion Criteria:** Children meeting the following inclusion criteria will be included: •IC1. Boys or girls, 6 months to 6 years of age; •IC2. With one of his/her parents/legal guardian purchases Petit Drill in a participating pharmacy in accordance with recommendations for use (regarding age and type of cough); •IC3. For infants between 6 months and 12 months of age – a confirmed prescription from a treating physician; •IC4. With an acute dry cough lasting less than 48 hours •IC5. With a score ≥ 3 at least for 3 of the 5 items of PCQ, (based on assessment of the night before inclusion); •IC6. For whom child-minding will allow to respect the recommended daily doses* of Petit Drill during the 3 day-treatment; •IC7. With a parent/legal guardian having a smartphone allowing using the ePRO App. NursTrial®; •IC8. With a parent/legal guardian able to understand and to complete to the questionnaires in timely manner; •IC9. With parent(s)/legal guardian who provide their signed informed consent for the child's enrolment in the study. ** 2-4 doses on D1, then 3 to 4 doses on D2 and D3, including one of the daily doses taken at bedtime.* **Exclusion Criteria:** Children meeting one of the following exclusion criteria will not be included: Presenting with one of the following conditions: • EC1. Presenting with one of the following conditions: o Chronic respiratory illness such as asthma, recurrent wheezing associated to viral infections and bronchitis; o Lower respiratory infections, such as bronchitis, bronchiolitis, and pneumonia;

	○ Angina, otitis, or sinusitis; ○ Persistent cough lasting more than 3 weeks, whatever the etiology; ○ Gastrointestinal pathology, involving vomiting, nausea, or diarrhoea. • EC2. With ongoing use of paracetamol and/or homeopathic products against cough; • EC3. Having had corticosteroid treatment, antibiotics, antihistaminic or any cough medication (such as, but not limited to, Phytoxil, Arkotoux) in the previous 15 days since inclusion; • EC4. With a brother/sister already included in the present clinical investigation*; • EC5. Enrolled in another clinical trial or being in a period of exclusion from a previous clinical trial. ** If several children are eligible in the same household, only one will be enrolled at random.*
Study endpoints/outcomes	**Primary outcome:** The primary outcome will be the percentage of children with a 3 point-decrease (minimal clinical significance) of the Pediatric Cough Questionnaire (PCQ) total score from baseline after up to 3 day-treatment with Petit Drill. The PCQ refers to a past night recall of 5 questions, each scored from 0 “Not at all” to 5 “Extremely” using a 6-point Likert scale. PCQ Total score consists of the sum of each score and ranges from 0 to 25. Baseline value will rate the night before the first day of treatment with Petit Drill, and will be recorded at inclusion (D1). Final value will rate the night following 3 day-treatment or the night following the day of stopping the treatment, and will be collected on the next morning. **Secondary outcomes:** • SO1. Baseline clinical and sociodemographic characteristics of children will be summarized using descriptive statistics. Secondary criteria related to the performance and the clinical benefit of Petit Drill will be described as follow: • SO2. Score global and score of the 5 items of PCQ (Q1: cough frequency, Q2: sleep disturbance of the child, Q3: sleep disturbance of the parent, Q4: cough severity, Q5: degree of bothersomeness to the child) will be described after 1, 2 and 3 day-treatment with Petit Drill. The percentage of children with a 3 point-decrease of PCQ total score from

	baseline at 1 and 2 day-treatment with Petit Drill will be described; • SO3. Daily cough severity will be measured using visual analogue scale (VAS) ranging from 0 (no cough) to 100 (worst cough) in response to "Yesterday, how was the cough of my child during the day?", measured VAS after 1, 2 and 3 day-treatment with Petit Drill. The evolution of the severity from baseline will be described; • SO4. Scores of the Parent-proxy Children's Acute Cough-Specific Questionnaire PAC-QoL (global and dimensions) will be collected at baseline (D1) and after 3 day-treatment with Petit Drill (morning D4), or on the next morning of the last day of treatment. The evolution of scores from baseline will be described. Secondary criteria related to the assessment of use and the safety of Petit Drill will be described as follow: • SO5. The mean (SD) number of times Petit Drill was administered in each 24-hour period from the first (D1) to the third (D3) day of treatment initiation will be described; • SO6. Parent's satisfaction with Petit Drill use will be described using a questionnaire, and responses measured using Likert scales. Responses will be presented as percentages; • SO7. Safety will be assessed by the analysis of: • Adverse events (frequency, severity, emergence, and causal relationship of adverse events) tabulated according to IMDRF terms (International Medical Device Regulators Forum, Annex E). Number and percentage of relevant AEs during treatment with Petit Drill, defined as all SAEs or AEs related to the device, and any AEs of special interest; • Number and percentage of device deficiencies. **Exploratory outcomes:** • SO8. The percentage of children receiving Petit Drill with or without physician prescription will be described by two age groups: from 6 months to 12 months old and from 13 months old to 6 years of age; • SO9. To assess all outcomes, except SO8, in the subgroup of children aged 6-24 months and subgroup of children aged 25 months to 6 years.
Brief description of the clinical investigation	**Pre-screening:**

	Pharmacist will briefly present the clinical investigation to the parent who purchases Petit Drill for his/her child from 6 months to 6 years old. A prescription will be mandatory for infant patients from 6 to 12 months old. If the parent does not want to participate but gives the pharmacist his/her agreement, the pharmacist will record in a pre-screened log child's age and gender, and main reason of parent's refusal. If the parent is interested, the pharmacist will provide the study information note and transfer the parent's name and contact information to the clinical investigation centre (CEN Expérimental). **Inclusion visit:** Upon receipt of a pre-screen patient, the parent will be contacted to take part to the remote inclusion visit with an Investigator (General Practitioner) of CEN Experimental, scheduled within the day of Petit Drill delivery. Before proceeding with the signing of the consent, the Investigator will first ensure that the parent is duly informed. Consent will be electronically signed using a solution (DocuSign) whose functionality meets recommended expectations of the Guidance on computerized systems and electronic data in clinical trials (EMA/INS/GCP/112288/2023). In non-single-parent households, the informed parent who signed the consent will remain the one who completes the study data in the ePRO App NursTrial®. If several children are eligible in the same household, an algorithm will randomly select one of them. Then, the Investigator will check the inclusion and exclusion criteria, and proceed to the patient's enrolment. The Investigator will record the necessary study data in the e-CRF (socio-demographics, baseline medical data). A Clinical Research Associate will help the parent download the NursTrial® App on their smartphone and create their personal access. Then, the parent will complete the study questionnaires in the App. **Study follow-up:** The patient's follow-up will last as long as he/she receives Petit Drill but will not exceed 3 days and 3 nights. During the follow-up, the patient's parent will have to complete the daily questionnaire and record Petit Drill intake in the App. Parents will be asked to inform the Investigator of any adverse event as soon as possible.
Statistical Methods	**Method:** The statistical analysis will be conducted in accordance with the protocol, and the Statistical Analysis Plan (SAP) which will precisely indicate the calculation of the variables, the populations studied (performance and safety), descriptive statistics, safety, handling of missing data. The SAP will be written as a separate document and approved prior to data review.

	The data review will aim to comprehensively review the data and record decisions regarding the handling of outliers, and if necessary missing data. **Analysis sets:** The full set will be made up of all enrolled patients. The safety population will be made up of all patients who have used Petit Drill at least once. The performance population will be made up of all patients for whom at least one evaluation of the primary outcome is available. **Statistical analyses:** All study outcomes will be analyzed using descriptive statistics. Continuous variables will be described by the mean, standard deviation (SD), median and range and quartile (Q1 and Q3). Some continuous variables may be converted to categorical variables, for which the numbers and increments may be defined in a more detailed statistical analysis plan (SAP). Categorical and ordinal variables will be described by the number and percentage of patients in each category, and the number and percentage of patients with missing information. Confidence intervals of 95% will be calculated for the primary outcome and the safety secondary outcomes. **Missing data:** In case of missing data or loss to follow-up, sensitivity analyses could be carried out to estimate the impact of missing data on the primary outcome.

2 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

2.1 Summary Description of the investigational device

Oropharyngeal Mucosa Protection Material PR2506 is a clear and colorless syrup with a strawberry flavor presented in a 125 ml bottle. The syrup is for oral use and to be applied with a measuring pipette. The 5 ml measuring pipette is included for dosing the oral solution.

Oropharyngeal Mucosa Protection Material PR2506 is a class IIa device following Rule 5 and Rule 21 of the new MDR. The applicable EMDN code for the syrup is Q0399: ENT DEVICES – OTHERS.

The pipette is a class Im device with measuring function following rule 1 of the Medical Device Directive (MDD) 93/42/EEC. The measurement function of the pipette has been validated by Rovipharm, for 60 uses (DT-034-PFM-324). The pipette falls under EMDN code A99 – DEVICES FOR ADMINISTRATION, WITHDRAWAL AND COLLECTION – OTHER.

Oropharyngeal Mucosa Protection Material PR2506 was initially CE marked by Pierre Fabre in 2013.

2.2 Manufacturer of the Investigational Device

The legal manufacturer of the syrup is:
Pierre Fabre Médicament
Les Cauquillous
81500 Lavaur, France

The legal manufacturer of the measuring pipette is:
Rovipharm
ZA de Lucinges
86 route du plan d'eau,
01370 Val-Revermont, France.

The procedure pack is assembled by:
Pierre Fabre Médicament
Les Cauquillous
81500 Lavaur, France

2.3 Model/type of the Investigational Device

Oropharyngeal Mucosa Protection Material PR2506

2.4 Traceability

Not applicable, as the product is commercialized (per Annexe I, clause 7 d) 2) of the EN ISO 14155 2020).

2.5 Intended Purpose

The intended use is the treatment of throat irritation (sore throat) associated with dry cough for infants starting at 6 months of age and in children up to 6 years of age.

2.6 Populations and Indications

Treatment of throat irritation (sore throat) associated with dry cough for infants from 6 months of age and in children up to 6 years of age.

2.7 Clinical, Technical and Biological Description of the Investigational Device

Description of the investigational device, including any materials, that will be in contact with tissues or body fluids. This shall include details of any medicinal substances, human or animal tissues or their derivatives, or other biologically active substances and reference to compliance with applicable national regulations.

The primary component of this syrup is glycerol (0.75 mL/5 mL). Table 1 provides further information with regards to the product's composition.

Table 1: Composition of the Petit Drill Syrup

Ingredient	Function	Specifications	% (g/ 100 ml)	Quantity per bottle (g)	Quantity per pilot batch (kg)	Quantity per batch (kg)
Glycerol 99.5%	Emollient	Eur.Ph (Monograph No.0496)	18.90%	23.625	37.8	378
Maltitol liquid	Sweetener	Eur.Ph (Monograph No.1236)	15.00%	18.75	30	300
Hydroxyethylcellulose	Thickening and viscosity increasing agent	Eur.Ph (Monograph No.0336)	0.60%	0.75	1.2	12
Sodium benzoate	Preservative	Eur.Ph (Monograph No.0123)	0.10%	0.125	0.2	2
Citric acid monohydrate	Antioxidant	Eur.Ph (Monograph No.0456)	0.50%	0.625	1	10
Sodium citrate	Buffering agent	Eur.Ph (Monograph No.0412)	0.40%	0.5	0.8	8
Strawberry flavour	Flavour enhancer	In House	0.15%	0.188	0.3	3
Purified water	Solvent	Eur.Ph (Monograph No.0008) + In house	-	qs 125Ml	qs 200L	qs 2000L
Total	**-**	**-**	**100.00**	**125 ml**	**200 L**	**2000L**

Oropharyngeal Mucosa Protection Material PR2506 forms a protective film and keeps throat moisturized due among others to the properties of glycerol. Under physiological conditions, a thin layer of watery mucus covers the throat and helps to keep it moist and lubricated. However, environmental influences,

systemic conditions or disease states may lead to pharyngeal dryness and increased viscosity, thickness and tackiness of secretions, which may provoke discomfort and cough [3].

The medical device presented here achieves its intended purpose by means of its main component glycerol which is a well-known demulcent agent. The efficacy of glycerol is related to its physical and chemical properties, as glycerol does not have any known pharmacological actions [4]. Indeed, hygroscopicity, or the ability to absorb moisture from the atmosphere/environment and hold it, is among the most valuable attributes of glycerol. Glycerol will absorb more than half of its weight of moisture when left exposed to the air. In addition, glycerol is characterized by a low volatility or low vapor pressure and high viscosity [4, 5]. These characteristics provide outstanding permanent humectancy, flexibility and plasticity.

Due to its properties (i.e., emollient/demulcent qualities and high viscosity), glycerol has the ability to form a soothing film covering the irritated mucous membrane of the throat and pharynx in patients suffering from cough. This coating film serves to lubricate and moisten the delicate pharyngeal mucosal tissues and to reduce the friction between moving surfaces of the pharynx and tongue, thus alleviating irritation while offering some protection from irritants such as smoke or dust particles. Glycerol may also influence the structure of the protein surface of the pharynx by decreasing the volume of proteins, and this may contribute to smoothing the surface and a lubricant effect. Overall, soothing of the throat helps reducing dry cough through a reduction of the afferent impulses from inflamed/irritated pharyngeal mucosa without centrally masking the cough reflex [4, 6-9].

In particular, a 2001 World Health Organization (WHO) report [9] states that demulcents may be useful to reduce cough associated with a dry throat in coating the throat and soothing irritated mucus membranes in children. It confirms the claimed mode of action by coating or lubrification of the posterior pharynx.

2.8 Training requirements

No special training is required to administer the product. The instructions for use (IFU) for this device explain how parents can give the treatment to their children using the pipette.

2.9 Special Medical Procedures

No special medical procedures are involved in the use of this device. Adult users should be able to administer the product to their children after reading the IFU. Petit Drill syrup, however, must be kept out of reach of children, especially the pipette.

2.10 Instructions for Use

The IFU for the device is provided in ANNEX I: IFU

Briefly, the device is recommended to be used up to 4 times in 24 hours, as needed. At each administration, a single dose of 5 mL is to be given to infants and children between 6 months and 6 years of age.

3 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

3.1 Background and Rationale

Coughing is one of the body's natural, necessary reflexes to clear the respiratory tract. It is triggered by the irritation of sensory nerves caused by the mechanical stimulation of the pharynx and tongue surfaces sliding over each other during swallowing and speech [4]. There are different kinds of cough: "productive" cough, associated with expectorations (mucus secretions), or dry cough, called "non-productive," without expectoration.

Dry cough is accompanied by a stinging sensation in the throat which generally intensifies at night, lying down, deteriorating the quality of life (QoL). Approximately one in ten of the population suffers from chronic cough, half of it interfering with daily activities [10]. Cough in children is different from that in adults in terms of duration, presentation, etiology and management. Common causes of acute cough in children are viral upper respiratory tract infections (URTI) and acute bronchitis, possibly associated to a pulmonary consolidation (medical diagnosis by thoracis auscultation (pulmonary rales such as crackles). In school children, URTIs with cough typically occurs 7-10 times per year [1].

An ideal cough treatment for children should relieve symptoms without any serious adverse effect and should not mask concomitant infection. Current cough management alternatives for the target population (from 6 months to 6 years of age) include medicinal products, medical devices or herbal preparations, available over the counter (OTC) or under prescription, which are based on various modes of action [9]. These include:

- Cough relieving products:
  - Centrally acting cough suppressants: codeine & other opiate derivatives, dextromethorphan, antihistamines, corticosteroids and steroids;
  - Soothing remedies: demulcents, including glycerol preparations;
  - Clearing products: expectorants, mucolytics, oral hydration and mist therapy.
- Natural remedies, such as lemon, honey, eucalyptus, etc.

3.1.1 Risks associated with existing cough relief treatments

In 2007, the Nonprescription Drug Advisory Committee to the Food and Drug Administration (FDA) and Paediatric Committee voted for immediate action against the use of cough and cold medicines in children under the age of six because of their side-effects [1].

FDA does not recommend the use of these products in children below two years of age and withdrew some OTC cough products or restricted their use in children, especially those under the age of two years due to serious and life-threatening adverse effects [4, 11, 12]. Health Canada does not recommend their use in children below the age of six.

The risks and benefits of OTC cough remedies for children were reassessed by the Medicines and Healthcare products Regulatory Agency (MHRA) in 2009 [13], following which it was concluded that antitussives (dextromethorphan and pholcodine), expectorants (guaifenesin and ipecacuanha), nasal decongestants (ephedrine, oxymetazoline, phenylephrine, pseudoephedrine, and xylometazoline) and antihistamines (brompheniramine, chlorphenamine, diphenhydramine, doxylamine, promethazine, and triprolidine) should be prohibited in children under 6 years of age. These products may be administered in children between 6-12 years, subject to basic principles of best care and available in pharmacies where advice can be given.

3.1.2 Glycerol as an effective and safe alternative for dry cough management

The WHO [9] and MHRA [13] **recommend the use of soothing products in children under the age of 6 years as an alternative to medicinal products** with a negative benefit/risk ratio. Soothing syrups that contain demulcents like glycerol, have been reported to be frequently used and safe and it has been concluded that their use should be encouraged in children. The effect of the demulcents is attributed to the "coating" or lubrication of the posterior pharynx.

Glycerol does not have any known pharmacological actions, and its efficacy is related to its physical and chemical properties:

- Glycerol **coats** and **lubricates** the pharyngeal surface (demulcent and lubricant properties), thus helping in reducing the friction between moving surfaces while swallowing and speaking.
- Inflamed mucosal surfaces in the pharynx may also be soothed by the **moisturizing** properties of glycerol.
- Glycerol may also decrease the volume of proteins on the pharyngeal mucosa, which may contribute to the **lubricant** effect [4].
- The **sweet** taste in cough syrups has been suggested to influence the production of endogenous opioids and therefore modulate cough at the level of the nucleus tractus solitarius [4].

The safety profile of glycerol is well known and has been documented since the beginning of its use in therapy, as an excipient in medicinal products or as an ingredient in the agro-alimentary industry. No significant toxicity has been reported following prolonged use of glycerol in humans. Glycerol is rapidly incorporated in standard metabolic pathways where it is completely bio-transformed by the body to endogenous compounds.

3.1.3 Rationale

Petit Drill is a clear and colorless syrup, consisting of glycerol (0.75mL/5mL or 15% v/v) presented in an amber glass bottle of type III (Eur. Pharm.3.2.1.), intended to be filled with 125 mL solution, with polypropylene child resistant closure. A 5 mL measuring pipette is included with Petit Drill, for dosing the oral solution.

Petit Drill was initially CE marked in 2013 under the Medical Devices Directive 93/42/EEC as Class I medical device. Due to new classification rules under the Regulation (UE) 2017/745 (MDR), it has been upgraded to Class IIa.

The clinical evaluation of this device has been categorized as a "Well Established Technology" according to MDCG 2020-6 (April 2020). Nevertheless, Pierre Fabre Médicament wishes to generate its own clinical data of this product in a real-life context, in order to support the clinical evaluation.

3.2 Evaluation of relevant pre-clinical assessment

The toxicological profiles of all ingredients were evaluated on the basis of the quantitative formulation of Petit Drill cough syrup. All of the ingredients in the Petit Drill cough syrup are well characterized in analytical, microbiological and toxico-pharmacological contexts. A biological evaluation of Petit Drill cough syrup has been conducted in conformity among others to the requirements of EN ISO 10993-1, EN ISO 10993-5, EN ISO 10993-9 and EN ISO 10993-10.

Results from the literature review performed on each component to evaluate the different biological endpoints identified in the risk management process according to EN ISO 10993-1, indicate that Petit

Drill cough syrup is not expected to induce cytotoxicity, sensitization or irritation. The local tolerance of the medical device was confirmed in biocompatibility studies (Biological Evaluation Report DT-034-PFM-630).

3.3 Evaluation of relevant clinical data

3.3.1 Description of the pathology

Coughing is one the body's natural, necessary reflexes to clear the respiratory tract. There are different kinds of cough: chesty cough, called "productive", associated with expectorations (mucus secretions), or dry cough, called "non-productive", without expectoration. Dry cough is accompanied by a stinging sensation in the throat which generally intensifies at night, deteriorating the patient's quality of life.

3.3.2 Data issued from clinical published studies on similar devices

No clinical trials on demulcent glycerol-based syrups are available in the pediatric population affected by acute cough. A single sponsored limited randomized, placebo-controlled trial investigating glycerol in adult patients suffering from dry cough is cited in the systematic review conducted by the Italian Society of Pediatric Allergy and Immunology for Acute cough in children and adolescents published in 2021 [14]. This trial was sponsored by Naturveda Laboratory [4]. The experimental device is described as a hypertonic, highly osmotic, filmogen glycerol-based spray. The main inclusion criteria were: patients male and female in the 18-65 years age group presenting all clinical signs and symptoms of severe dry cough, sore throat with pain, and inflammation. The authors report that the group receiving the experimental filmogen glycerol-based spray showed a significant decrease in the mean scores of dry cough severity and frequency, throat pain, irritation, swelling, and redness when compared to saline placebo spray. No further details are given for the experimental formula. It is unknown if this experimental spray has obtained "market clearance".

Although, no clinical data are available in the pediatric population, cough syrups containing glycerol are promoted as the first-choice of cough treatment in infants and children up to 6 years old by health organizations (such as the WHO [9] and MHRA [13]) and professional guidelines.

Evidence-based reviews, systematic reviews and guidelines demonstrate the physiological effect of glycerol demulcent, thus establishing the ability of the demulcent to soothe the throat and to reduce symptoms of coughing.

3.3.3 Data issued from clinical investigations on the device

Pierre Fabre participated in the MAGICIA study [15] (MAnagement of couGh for Infants and Children during Infections of Airways). This study aimed at assessing the impact of acute cough on patients' and parents' sleep and children's activities in four European countries (Greece, Poland, Belgium and Portugal). MAGICIA study [15] was not designed explicitly for the evaluation of Petit Drill (known as Balsokids in Belgium). The benefits of Petit Drill could not be evaluated in the MAGICIA study because of the concomitant use of other medications in included patients.

The MAGICIA had a follow-up period of one week. The main objective of the study was to assess the impact of acute dry or mixed cough on the patient's and parents' sleep and activities. Secondary objectives included: evaluation the social impact of acute cough, description of symptoms associated with acute cough, of the therapeutic management of acute cough by pediatricians and general practitioners in each country, of cough evolution on one-week follow-up, of parents' observance and

satisfaction with treatment and therapeutic management, and of the profile of patients suffering from acute cough.

Children aged six months to six years visiting their general practitioner or pediatrician for common upper respiratory infections associated with acute dry or mixed cough, for up to three days before physician examination, were included. Exclusion criteria included receipt of antibiotics or corticosteroids during the past two weeks, diagnosis of chronic disease and need for hospitalization. These criteria aimed at including only patients with acute banal cough secondary to common viral infections without complications.

Ethical approval of this study was obtained from the relevant local ethics committees in Belgium, Portugal and Greece. Ethics approval was not required in Poland. Parental written informed consents were obtained, and all data were stored in an anonymous form.

The study included 1239 children (mean age: 3.1±1.7 years) aged six months to six years. Medicinal products were often prescribed (83.6–99.6% of the patients), mainly demulcent syrup (except in Portugal) and antipyretics, while active antitussives with pharmacological agents were less often prescribed. In Portugal, a high proportion of patients (46.5%) received antibiotics compared to the three other countries. Petit Drill (or Balsokids) was reported as having been taken by patients in 218 children (49.6%) in Greece, 257 (55.3%) in Poland, 73 (47.7%) in Belgium and in none in Portugal; that is, a total of 548 patients of 3.1 (±1.7) years, (44.2% of the cohort of 1239).

As most of the children (n=474) received other medications as well, it was not possible to evaluate the efficacy of glycerol syrup. However, 115 patients were prescribed only saline rinses and glycerol syrup as a treatment for cough, and 74 took only glycerol syrup between D0 and D7. The profile of the patients receiving glycerol syrup alone seems to be children with fewer symptoms such as fever, runny nose, nasal congestion, body aches, sore throat or ear pain, diarrhea, vomiting or reduced appetite. Compliance was high; 82.1% in Greece, 96.8% in Poland, 91.6% in Belgium and 89.3% in Portugal. When Petit Drill was prescribed, compliance was 83% in Belgium, 91% in Poland and 95% in Greece; this brand was not prescribed in Portugal.

Overall, at D0, cough frequency was reported as occasional in 26.9% of patients; frequent in 60.1%, and almost permanent in 12.9%. This decreased over time, being occasional at D7 in 89.8% of patients, frequent in 9.4% and almost permanent in 0.9%. At D0, cough intensity was mild in 23.7% of patients, moderate for 54.3% and severe for 22.0%, while these frequencies were 87.6%, 10.6% and 1.8%, respectively at D7.

Parents' satisfaction was assessed using the Client Satisfaction Questionnaire which includes eight questions (CSQ-8) related to initial information and advice, therapeutic management, with score ranging from 8 (very dissatisfied) to 32 (very satisfied) or on a visual analogue scale (0–10). At D7, the CSQ-8 scores evaluating parents' satisfaction ranged from 17 to 32 (maximum value of the score). The mean score in the three countries using the CSQ-8 was 27.8/32. Specifically, the mean CSQ-8 score was 29.5 in Greece, 28.3 in Poland and 21.7 in Belgium. In Portugal, satisfaction was assessed with a visual analogue scale and the mean score was 9.2 out of 10. The mean CSQ-8 score assessing parents' satisfaction for the population of children who received only glycerol syrup was 29.6 (out of 32), which was slightly higher than the country-wise mean satisfaction scores obtained in children who also received other treatments (21.7–29.5).

No complaints or vigilance cases related to the intake of glycerol syrup have been reported in any of the four countries. Additionally, this study confirms the absence of undesirable side effects due to possible interactions of demulcent syrups with drugs.

3.3.4 Safety data recorded from vigilance records

The tested product is already CE marked and has been on the market in several European countries since 2013. Up to 31-Aug-20232023, 47 cases were received for the tested product. Only 11 cases were associated with adverse reactions and all were assessed as non-serious.

The recorded safety data did not highlight any safety concern and showed good tolerability of the product.

3.4 Clinical development stage

This is a post-market clinical investigation, which aims to confirm clinical safety and performance data on the Petit Drill® Syrup.

4 RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

4.1 Anticipated clinical benefits

The anticipated clinical benefits are not different to those claimed in the IFU of the device.
Petit Drill® Syrup soothes the irritation associated with dry cough by coating and moisturizing the throat. Due to its composition, Petit Drill® Syrup forms a protective film and moisturizes the throat, which makes it possible to calm the irritation and sore throat associated with dry cough.

4.2 Anticipated adverse device effects

Risks associated with the investigational device and its related clinical procedure shall be estimated in accordance with EN ISO 14971 prior to design and conduct of a clinical investigation (see Annex H of EN ISO 14155-2020). The risk assessment shall include or refer to an objective review of published and available unpublished medical and scientific data.

A summary of the benefit-risk analysis shall be disclosed in the relevant clinical investigation documents. The CIP shall include all anticipated adverse device effects and a rationale for the related benefit-risk ratio (see Annex A of EN ISO 14155-2020).
The risk assessment is provided in the Petit Drill Product Risk Management document DT-034-PFM-520-01, which is provided in ANNEX II: DT-034-PFM-520-01 Product risk management.

4.3 Risks associated with participation in the clinical investigation

The participants in this clinical investigation will not be exposed to any additional risks than those disclosed in the above sections, as this device is intended to be used as described in the IFU and in real-life practice.

4.4 Possible interactions with concomitant medical treatments

None known to date.

4.5 Actions to control or mitigate risks

These actions have been detailed in the Petit Drill Product Risk Management document DT-034-PFM-520-01, which is provided in ANNEX II: DT-034-PFM-520-01 Product risk management.
Most identified risks could be mitigated by following the instructions for usage and safe storage of the device, that have been elaborated in the IFU (ANNEX I: IFU).

4.6 Risk-to-benefit rationale

There will be no additional benefits or risks to the patient participating in the investigation, as it is a real-life observational study in which the device will be used per the IFU.

The results of this investigation would be essential for obtaining clinical data on device performance and safety, which will be utilized to support the clinical evaluation of the device as it is upgraded from a Class I to a Class IIa device, per the MDR, as explained in section 3.1.3.

No potential threats to this observational study have been identified, and no interactions with concomitant interventions are anticipated, other than those addressed in sections 4.2 and 4.3.

5 OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

The objective of this investigation is to obtain real-life clinical safety and performance data to support the current clinical evaluation of the Petit Drill device.

5.1 Objectives

5.1.1 Primary objective

To assess the performance of the Petit Drill medical device in the treatment of throat irritation (sore throat) associated with dry cough in infants starting at 6 months of age and in children up to 6 years of age.

5.1.2 Secondary objectives

- SO1. To describe the clinical and sociodemographic characteristics of children using Petit Drill.

The following secondary objectives will describe the performance and clinical benefit of Petit Drill in terms of:

- SO2. Changes in nightly cough frequency, severity, bothersome for the child, and ability to sleep for child and parent(s) throughout the 3 day-treatment;
- SO3. Changes in daily cough severity;
- SO4. Evolution of Quality of life.

The following secondary objectives will describe the use and safety of Petit Drill:

- SO5. Adherence to use of Petit Drill Syrup;
- SO6. Parents' satisfaction with Petit Drill use;
- SO7. Safety of the Petit Drill medical device in infants aged from 6 months to children up to 6 years of age.

5.1.3 Exploratory objectives

- SO8. To describe the dispensing modalities of Petit Drill by age group;
- SO9. To describe the study objectives (except SO8) according to child's range of age.

5.2 Hypotheses (if applicable)

Since this is an observational study, there are no formal hypotheses to test.

5.3 Risks and anticipated adverse device effects to be assessed

No additional risks or anticipated device effects were observed since the first CE mark application, apart from the ones already known or identified. Clinical safety data for Petit Drill will be obtained for the first time as part of a clinical investigation.

6 CLINICAL INVESTIGATION DESIGN

6.1 Type of clinical investigation

This will be an observational, prospective, single-arm descriptive clinical investigation, monocentric with national (French) patient pre-screening, which will not mandate or recommend any additional interventions or in-person visits. Since Petit Drill is an OTC treatment, patient contact, eligibility pre-screening will occur via pharmacies selling this device. Enrolment of the patients will be conducted remotely by the investigators (General Practitioners) of the Clinical Investigation Centre CEN Experimental located in DIJON (France).

All decisions regarding the treatment of included patients could be made by the investigators, dispensing pharmacist, and prescribing physician where applicable. All patients will be treated according to the local clinical practice and their parent/legal guardian will be instructed to fill questionnaires via a mobile application at specific timepoints.

The investigation and data collection are patient centered. The secure mobile application for PRO NursTrial® will be used to allow parents/ legal guardians to record the following data:

- Any AEs that may occur during the 3-day/3-night follow-up period;
- The number of times Petit Drill was administered to the patient on a daily basis;
- Patient-reported outcomes (PRO) – questionnaires to be filled by the patient to provide their assessment of the performance and useability of the device and their quality of life.

6.2 Bias minimization

1) **Site and patient selection bias:** Parent/legal representative of patients who refuse to participate may limit the representativeness of the study results. A screening log (see section 6.4) will be maintained, which will capture selected details from patients who were excluded or who parent/legal representative refused to participate, in order to counter this limitation. Another aspect is that this device can be purchased online, whereas recruitment will only be carried out via pharmacies. Therefore, patients who use Petit Drill syrup through online purchases will not be covered by this study.

2) **Attrition bias:** patients lost to follow-up are the main source of attrition bias in cohort studies. This can threaten sample representativeness if too many patients are lost to follow-up or if they differ from patients continuing follow-up (such as in their baseline characteristics or in their outcomes). To minimize any risks and potential impact, efforts will be undertaken to collect the data from the lost-to-follow up patient's most recent data recording, and investigators will be encouraged to contact the patient for a discontinuation assessment. Baseline characteristics of patients lost-to-follow up and those who completed the investigation may also be described to assess representativeness. Nevertheless, the follow-up period for this investigation is very short (3 days), the mobile application will send alerts resulting in parent/legal representative recall. Taken together, these measures are expected to minimize attrition bias.

3) **Recall bias:** is an inherent limitation of recollections from events or experiences from the past. This may apply to data collected for certain time periods in the past, such as the onset of improvement following treatment administration from the previous night. Since the periods of recall for this investigation will be very short, the impact of this bias will be minimized. Additionally, parents will be briefed on important timepoints from which data is to be retained so they are aware of the most

important information that needs to be retained for recording. As just mentioned above, missing data will result in alerts and recall of parent/legal representative.

4) **Measurement error and missing data:** This investigation relies on the patients' parents recording data for most study outcomes. Since they are not trained professionals and not used to responding to medical questionnaires, human error is to be anticipated in the estimation of numerical data, in the interpretation of questionnaires and in the recording of information. Measures will be put in place during eCRF and the mobile application NursTrial® to minimize these errors. The following quality checks are anticipated:

   - Limiting the use of free fields for data entry – limiting responses to multiple choice questions, or list selection;
   - Prompts and reminders in case of missing data.

   In case of missing data or loss to follow-up, sensitivity analyses could be carried out to estimate the impact of missing data on the primary outcome.

6.3 Outcomes

6.3.1 Primary outcome

The primary outcome will be the percentage of children with a 3 point-decrease (minimal clinical significance) of the Pediatric Cough Questionnaire (PCQ) total score from baseline after up to 3 day-treatment with Petit Drill.

The PCQ refers to a past night recall of 5 questions, each scored from 0 "Not at all" to 5 "Extremely" using a 6-point Likert scale. PCQ Total score consists of the sum of each score and ranges from 0 to 25.

Baseline value will rate the night before the first day of treatment with Petit Drill, and will be recorded at inclusion (D1).

Final value will rate the night following 3 day-treatment or the night following the day of stopping the treatment, and will be collected on the next morning.

6.3.2 Secondary outcome(s)

- SO1. Baseline clinical and sociodemographic characteristics of children will be summarized using descriptive statistics;

Secondary criteria related to the performance and the clinical benefit of Petit Drill will be described as follow:

- SO2. Score global and score of the 5 items of PCQ (Q1: cough frequency, Q2: sleep disturbance of the child, Q3: sleep disturbance of the parent, Q4: cough severity, Q5: degree of bothersomeness to the child) will be described after 1, 2 and 3 day-treatment with Petit Drill. The percentage of children with a 3 point-decrease of PCQ total score from baseline at 1 and 2 day-treatment with Petit Drill will be described;
- SO3. Daily cough severity will be measured using visual analogue scale (VAS) ranging from 0 (no cough) to 100 (worst cough) in response to "Yesterday, how was the cough of

my child during the day?", measured VAS after 1, 2 and 3 day-treatment with Petit Drill. the evolution of scores from baseline will be described;

- SO4. Scores of the Parent-proxy Children's Acute Cough-Specific Questionnaire PAC-QoL (global and dimensions) will be collected at baseline (D1) and after 3 day-treatment with Petit Drill (morning D4), or on the next morning of the last day of treatment. The evolution of scores from baseline will be described.

Secondary criteria related to the assessment of use and the safety of Petit Drill will be described as follow:

- SO5. The mean (SD) number of times Petit Drill was administered in each 24-hour period from the first (D1) to the third (D3) day of treatment initiation will be described;
- SO6. Parent's satisfaction with Petit Drill use will be described using a questionnaire, and responses measured using Likert scales. Responses will be presented as percentages;
- SO7. Safety will be assessed by the analysis of:
  - Adverse events (frequency, severity, emergence, and causal relationship of adverse events) tabulated according to IMDRF terms (International Medical Device Regulators Forum, Annex E). Number and percentage of relevant AEs during treatment with Petit Drill, defined as all SAEs or AEs related to the device, and any AEs of special interest;
  - Number and percentage of device deficiencies.

6.3.3 Exploratory outcomes

- SO8. The percentage of children receiving Petit Drill with or without physician prescription will be described by two age groups: from 6 months to 12 months old and from 13 months old to 6 years of age;
- SO9. To assess all outcomes, except SO8, in the subgroup of children aged 6-24 months and subgroup of children aged 25 months to 6 years.

PRO questionnaires in order to assess the user's perspective of the device's performance are given below. The variables for each questionnaire are detailed in section 6.4.

The Pediatric Cough Questionnaire (PCQ) (Annex III)
The PCQ is a reliable and validated questionnaire by Hartnick *et al.* [17]. The five questions, which could be answered by the child's parent or proxy, cover cough frequency (Q1), sleep disturbance of the child (Q2), sleep disturbance of the parent (Q3), cough severity (Q4), and the degree of bothersomeness to the child (Q5). Each of the five items was scored on a 6-point Likert scale, from 0 to 5, and possible over scores range from 0 to 25. The higher the scores, the higher the severity. A 3-point difference in PCQ score is clinically significant.

Parent-proxy Children's Acute Cought-Specific Questionnaire (PAC-QoL) (Annex IV)
The PAC-QoL instrument is an acute cough-specific QoL in young children, that measures the burden, of acute cough in children. Original PAC-QoL_{16} has been validated by Anderson-James *et al.* [18], then re-validated by Anderson-James *et al.* [19] concomitantly with the shorter form of 6 items (PAC-QoL_6), that has been found as robust and as reliable than the 16 item-form.
PAC-QoL_6 consisted of 6 items utilizing a 7-point Likert-type rating scale (1 = all the time or very, very worried and concerned to 7 = none of the time or not worried and concerned). Items referred to a 24-hour recall. Higher PAC-QoL scores reflect better QoL with lower scores reflecting greater frequency

and worries or concerns. The minimal clinical significance for the overall PAC-QoL$_6$ questionnaire is therefore estimated to be 0.71–1.11 [19].

Daily cough severity using an electronic VAS (Annex V)
Subjective assessment of cough severity using 0-100 VAS for rating cough severity (0: no cough to 100: worst cough) has been validated by Lee *et al*. [20]. In this clinical investigation, subjective assessment of cough severity will be performed using e-VAS thanks to NursTrial® App. Even length of the scale could vary depending on the screen of the patient' smartphone, electronic and paper VAS presented comparable results, as 100 mm length is not a requirement [21].

6.4 Variables

Variables to be collected in pre-screening log by the pharmacist:

- Patient age in years and months;
- Reason for non-inclusion to the investigation (if applicable). For example: antibiotics, previous cough treatment;
- Reason for refusal to participate in the investigation (if applicable).

Variables to be collected in screening log by the investigator:

- Patient age in years and months;
- Reason for non-inclusion to the investigation (if applicable);
- Approximate date of dry cough start;
- PCQ-score (based on the recall of the night prior inclusion) – only patients with a score of 3 or above at least for 3 of the 5 items of PCQ are to be included (see section 6.9.1).

Table 2: Variables to be collected at patient enrolment

Sociodemographic data and dispensing modalities	Age in years and months
(To be recorded by the investigator in the eCRF)	Rank among siblings
	Weight and height
	Sex and geographic region
	Did the patient receive a doctor's prescription for Petit Drill? (Yes/No)
Baseline medical data	Pre-existing medical conditions
(To be recorded by the investigator in the eCRF)	Investigator's assessment of patient's condition Acute dry cough Yes/No
	Approximate date of dry cough start
	Prior treatments for ongoing cough
	Ongoing, non-interfering medications
	Associated symptoms at baseline
	Fever (Yes/No)
	Runny nose (Yes/No)
	Congestion (Yes/No)
	Sore throat (Yes/No)
	Ear Pain (Yes/No)
	Sensation of pain or more frequent crying than usual (Yes/No)
	Digestive symptoms (vomiting or diarrhoea) (Yes/No
	Reduced appetite (Yes/No)
PCQ ***(to be recorded by the parent/legal representative in the NursTrial® app with the help of the investigator)***	

Q1. How frequent was your child's cough last night?	0- Not at all
	1- Occasionally
	2- A little
	3- Somewhat
	4- Very much
	5- Extremely
Q2. How much did last night's cough affect your child's ability to sleep?	0- Not at all
	1- Occasionally
	2- A little
	3- Somewhat
	4- Very much
	5- Extremely
Q3. How much did last night's cough affect your ability to sleep?	0- Not at all
	1- Occasionally
	2- A little
	3- Somewhat
	4- Very much
	5- Extremely
Q4. How severe was your child's cough last night?	0- Not at all
	1- Occasionally
	2- A little
	3- Somewhat
	4- Very much
	5- Extremely
Q5. How bothersome was last night's cough to your child?	0- Not at all
	1- Occasionally
	2- A little
	3- Somewhat
	4- Very much
	5- Extremely
PAC-QoL *(to be recorded by the parent/legal representative in the NursTrial® app with the help of the investigator)*	
1-Were you worried/concerned about your child's cough becoming worse?	1- very, very worried and concerned
	2- very, worried and concerned
	3- fairly, worried and concerned
	4- somewhat worried and concerned
	5- a little worried and concerned
	6- hardly worried and concerned
	7- not worried and concerned
2-Did you feel tired or exhausted because of your child's cough?	1- all the time
	2- most of the time
	3- quite often
	4- some of the time
	5- once in a while
	6- hardly any of the time
	7- none of the time
3-Were you worried/concerned about the effects of your child's cough on him/her?	1- very, very worried and concerned
	2- very worried and concerned
	3- fairly, worried and concerned
	4- somewhat worried and concerned
	5- a little worried and concerned
	6- hardly worried and concerned
	7- not worried and concerned
4-Were you worried/concerned about the cause of your child's cough?	1- very, very worried and concerned
	2- very worried and concerned

	3- fairly, worried and concerned
	4- somewhat worried and concerned
	5- a little worried and concerned
	6- hardly worried and concerned
	7- not worried and concerned
5-Were you worried/concerned about your child not sleeping well because of the cough?	1-very, very worried and concerned
	2- very worried and concerned
	3- fairly, worried and concerned
	4- somewhat worried and concerned
	5- a little worried and concerned
	6- hardly worried and concerned
	7- not worried and concerned
6- Did your family need to change plans because of your child's cough?	1-all the time
	2- most of the time
	3- quite often
	4- some of the time
	5- once in a while
	6- hardly any of the time
	7- none of the time
Daily cough severity ***(to be recorded by the parent/legal representative in the NursTrial® app with the help of the investigator)***	
"Yesterday, how was the cough of my child during the day?"	eVAS 0 _____100 No cough Worse cough

Table 3: Variables to be collected during patient follow-up by the parent/legal representative

Outcome	Suggested schedule	Variables
For primary outcome and secondary performance outcome 1: PCQ global and scores of the 5 items Q1, Q2, Q3, Q4 and Q5	D2 – first thing in the morning after 1st night of treatment D3 – first thing in the morning after 2nd night of treatment D4 – first thing in the morning after 3rd night of treatment	0 – Not at all 1 – Occasionally 2 – A little 3 – Somewhat 4 – Very much 5 – Extremely
For secondary performance outcome 2: Daily cough severity	D2 – first thing in the morning after 1st night of treatment D3 – first thing in the morning after 2nd night of treatment D4 – first thing in the morning after 3rd night of treatment	0-100 eVAS value
For secondary clinical benefit outcome: PAC-QoL	D4 – first thing in the morning after 3rd night of treatment	1- all the time or very, very worried and concerned 2- most of the time or very, worried and concerned 3- quite often or fairly, worried and concerned 4- some of the time or somewhat worried and concerned 5- once in a while or a little worried and concerned 6- hardly any of the time or hardly worried and concerned 7- none of the time or not worried and concerned
For secondary safety outcome: number and percentage of AEs, including device deficiencies (DD) (to be completed by the investigator during an interview with the parent/legal representative)	Once a day, at a time of choice and at investigation end.	All AEs during the 3-day period will be asked to be reported by the patient, whether they think it is related to the investigational device or not. Once a day the following questions will be asked. • **Today did your child experience any sort of illness or negative effects (whether related to the Syrup or not)?** Yes/ No **If yes, please contact the investigator.**

Outcome	Suggested schedule	Variables
Adherence	At least once a day or at each intake	How many times in the previous 24 hours did your child use Petit Drill? (Insert a single digit number) For each dose, please give the approximate time: HH:MM If Petit Drill is stopped before the recommended treatment duration of 3 days, please specify the reason: Cough improvement / Cough worsening / Other /Other specify
Parent Satisfaction with Petit Drill Syrup Use	At study end (after 3 days of use)	• How would you rate the quality of therapeutic management your child received? (Excellent/ Good/ Fair/ Poor) • To what extent did this treatment meet your child's needs? (Almost all of my child's needs were met/ Most of my child's needs were met/ Only few of my child's needs were met/ None of my child's needs were met) • Would you recommend this treatment to another parent? (No, definitely not/ Not really/ Yes, generally/ Yes, definitely) • How satisfied are you with information received from the IFU to use this treatment? (Quite dissatisfied/ Indifferent or mildly dissatisfied/ Mostly satisfied/ Very satisfied) • In a general sense, was it easy to use this treatment? (No, definitely not/ Not really/ Yes, generally/ Yes, definitely) • Did your child seem to like the taste of the syrup? (No, definitely not/ Not really/ Yes, generally/ Yes, definitely)

Table 4: Variables to be collected by the investigator in case of AE or DD occurring during patient follow-up

Outcome	Suggested schedule	Variables
For secondary safety outcome: number and percentage of AEs, including device deficiencies (DD) (to be completed by the investigator during an interview with the parent/legal representative)	Anytime during patient's follow-up	**Select all that apply** • Any new illness or symptom (diagnosed or undiagnosed) • Any worsening of an existing illness or symptoms (diagnosed or undiagnosed) • Any medical interventions (such as vaccination, surgery etc.) • Any usual or unusual health-related event (such as loss of appetite, teething pain, reflux etc.) **For each event, please provide the following details:** • **Describe event in own words** • **Date of event start:** DD/MM/YYYY • **Action taken in response to event (select all that apply):** medications given/ hospitalization/ visit to a healthcare professional (HCP)/ no action taken • **Assessment of seriousness:** • Did the event lead to death? Yes/ No • Did the event lead to a life-threatening illness or injury? Yes/ No • Did the event lead to permanent impairment of a body part or body function? Yes/ No • Did the event lead to hospitalization or prolongation/ Yes/ No • Did the event require a medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body part or body function? Yes/ No • Did the event lead to development of a chronic disease? Yes/No • **Outcome at the end of the 3-day follow-up** (select only ONE): Ongoing/ Completely Resolved/ Resolved with after-effects/ Not sure • Please select all that apply regarding the use of Petit Drill • The external packaging was damaged upon reception • The bottle cap was not sealed, or damaged upon reception • The bottle was damaged upon reception/during use • The pipette was damaged upon reception • The pipette was damaged during use • I used more or less than the prescribed dose because it was confusing to use the pipette

		• I used more or less than the prescribed dose because the IFU was not clear • The syrup fell into eyes or ears during use • My child was taking another medication while using the syrup If yes, please mention the medication • My child may be allergic to the syrup • Someone else, other than my child used the syrup (including accidental use) • Child accidently accesses the bottle • I did not use the designated pipette • Syrup reached air tube • Pipette reached air tube

6.5 Replacement of subjects

Not applicable.

6.6 Investigation sites

Patient pre-screening will occur via pharmacies. Around one hundred and twenty-five pharmacies throughout France will be required to participate in this investigation to reach the required patient number (see section 6.9.6).

6.7 Clinical investigation end

A patient accrual period of 6 to 9 months is estimated to achieve the targeted sample size of 245 patients (see section 6.9.6). Given that the patient follow-up period is only 3 days, the length of the investigation will also be around 6 to 9 months.

6.8 Investigational device(s) and comparators

The investigational device is Petit Drill® Syrup by Pierre Fabre Médicament.
No comparators are to be used in this single-arm observational study.

6.8.1 Exposure

Not applicable.

6.8.2 Justification of the choice of comparator

Not applicable.

6.8.3 Other needed medical device or medication

Pipette to dispense the syrup is provided with the investigational device, as described in section 2.1.

6.8.4 Number of investigational devices to be used

Only one investigational device will be assessed in this clinical investigation: the Petit Drill® Syrup. The device is to be used per the IFU.

6.9 Subjects

If the parent/legal representative does not want to participate but gives the pharmacist his/her agreement for pseudonymous data collection of his/her response, the pharmacist will record in a pre-screened log the following data in the study website:

- Patient age in years and months;
- Reason for refusal to participate in the investigation (if applicable);
- Reason for non-inclusion to the investigation (if applicable, i.e., patient not meeting a main entry criteria).

6.9.1 Inclusion criteria

Children meeting the following inclusion criteria will be included:

- IC1. Boys or girls, 6 months to 6 years of age;
- IC2. With one of his/her parents/legal guardian purchases Petit Drill in a participating pharmacy in accordance with recommendations for use (regarding age and type of cough);
- IC3. For infants between 6 months and 12 months of age – a confirmed prescription from a treating physician;
- IC4. With an acute cough lasting less than 48 hours
- IC5. With a score ≥ 3 at least for 3 of the 5 items of PCQ, (based on assessment of the night before inclusion);
- IC6. For whom child-minding will allow to respect the recommended daily doses* of Petit Drill during the 3 day-treatment;
- IC7. With a parent/legal guardian having a smartphone allowing using the ePRO App. NursTrial®;
- IC8. With a parent/legal guardian able to understand and to complete to the questionnaires in timely manner;
- IC9. With parent(s)/legal guardian who provide their signed informed consent for the child's enrolment in the study.

** 2-4 doses on D1, then 3 to 4 doses on D2 and D3, including one of the daily doses taken at bedtime.*

6.9.2 Exclusion criteria

Children meeting one of the following exclusion criteria will not be included:

- EC1. Presenting with one of the following conditions:
  - Chronic respiratory illness such as asthma, recurrent wheezing associated to viral infections and bronchitis;
  - Lower respiratory infections, such as bronchitis, bronchiolitis, and pneumonia;
  - Angina, otitis, or sinusitis;
  - Persistent cough lasting more than 3 weeks, whatever the etiology;
  - Gastrointestinal pathology, involving vomiting, nausea, or diarrhoea.
- EC2. With ongoing use of paracetamol, and/or homeopathic products against cough;
- EC3. Having had corticosteroid treatment, antibiotics, antihistaminic or any cough medication (such as, but not limited to, Phytoxil, Arkotoux) in the previous 15 days since inclusion;
- EC4. With a brother/sister already included in the present clinical investigation*;
- EC5. Enrolled in another clinical trial or being in a period of exclusion from a previous clinical trial.

** If several children are eligible in the same household, only one will be enrolled at random.*

6.9.3 Subject withdrawal and lost-to-follow-up

The risk of loss-to follow-up in this investigation is minimal due to the very short follow-up duration of 3 days, which is the recommended treatment duration per the Petit Drill® Syrup IFU.

Nevertheless, a subject will not be prevented from withdrawing their parent/legal representative consent at any time between enrolment and the 3 days of participation, whereby the subject will be withdrawn from the investigation and no further data will be collected. In each case, reasons for withdrawing their consent will be obtained.

6.9.4 Expected duration of the clinical investigation

This will be equal to the length of the planned accrual period of 6-9 months, as the follow-up duration for each patient is only 3 days long.

6.9.5 Expected duration of each subject's participation

Subjects will be followed-up for 3 days since the initiation of the Petit Drill® syrup intervention.

6.9.6 Sample size

A sample size of 245 patients is proposed for this clinical investigation, considering a dropout rate of 20% (see section 7.4). The rationale for this sample size is discussed in section 7.4 below.

6.9.7 Period and point of enrolment

Patients will be recruited from participating pharmacies throughout metropolitan France. The maximum recruitment period will be at least from November 2023, over a period of 6 to 9 months.

Based on sales numbers, a monthly sales rate of 4 units per pharmacy was estimated for Petit Drill® Syrup in France. Considering around 125 sites will be recruited, and a 25% participation acceptance rate (optimal scenario) upon proposal of the clinical investigation, a patient accrual period of 3 months during the winter season should permit reaching the targeted sample size.
However, since this is a real-life study and that the participation acceptance rate may have been overestimated, enrollment period is extended by 6 to 9 months.

6.9.8 The investigation population relative to the target population

The Petit Drill® Syrup is intended to be used for the treatment of throat irritation (sore throat) associated with dry cough in infants from 6 months of age and in children up to 6 years of age.
Minimum exclusion criteria have been defined for the selection of patients, so that the most representative sample can be included in the study. Nevertheless, for the purpose of proving the performance of the device certain selection criteria had to be implemented, which will mean that certain characteristics of the investigation population will be slightly different to the target population. These selection criteria include:

- Inclusion of patients only with score ≥ 3 at least for 3 of the 5 items of PCQ, (based on the recall of the night prior inclusion), which means milder forms of cough will not be investigated;
- Exclusion of patients taking concomitant treatments, up to 15 days before Petit Drill start, that may interfere with or mask Petit Drill® device's performance, such as paracetamol, anti-histamines, steroids, antibiotics or cough medication;
- Exclusion of patients with chronic respiratory conditions (such as asthma or bronchitis) and persistent cough lasting more than 3 weeks;
- Patients with lower respiratory infections, such as bronchitis, bronchiolitis and pneumonia;
- Angina, otitis, or sinusitis;
- Gastrointestinal pathology, involving vomiting, nausea, or diarrhoea.

Nevertheless, the differences between the investigation and target population are not so large that it would impact the overall transposability of clinical performance and safety data to the general target population.

6.9.9 Vulnerable populations

Petit Drill® Syrup is intended to be used in a vulnerable population, i.e., paediatric patients from 6 months to 6 years of age.
Since this is a real-life investigation, patients will not be required to undergo any additional procedures or interventions, apart from those defined in the Petit Drill® Syrup IFU. Furthermore, the parent(s) or legal guardians of children will be informed in detail about the investigation, and the benefits and risks to their ward of participating in it, prior to obtaining their written consent.

6.10 Procedures

Pre-screening

Pharmacist will briefly present the clinical investigation to the parent/legal representative who purchases Petit Drill for his/her child/relative from 6 months to 6 years old. The pharmacist will also orally verify the eligibility criteria (Cf. sections 6.9.1 and 6.9.2).

If the parent does not want to participate but gives the pharmacist his/her agreement, the pharmacist will record in a pre-screened log child's age and gender, and main reason of parent's refusal.

If the parent is interested, the pharmacist will provide the study information note and transfer the parent's name and contact information to the clinical investigation centre (CEN Expérimental) via a dedicated page of the study website.

Inclusion visit

Upon receipt of a pre-screen patient on the study website, the parent/legal representative will be contacted to take part to the remote inclusion visit with an Investigator (General Practitioner) of CEN Experimental, scheduled within the day of Petit Drill delivery.

Before proceeding with the signing of the consent, the investigator will first ensure that the parent/legal representative is duly informed. Consent will be electronically signed using a solution (DocuSign) whose functionality meets recommended expectations of the Guidance on computerized systems and electronic data in clinical trials (EMA/INS/GCP/112288/2023). The informed consent process is detailed in section 13.

In non-single-parent households, the informed parent who signed the consent will remain the one who completes the study data in the ePRO App NursTrial®.

If several children are eligible in the same household, an algorithm will randomly select one of them. Then, the Investigator will check the inclusion and exclusion criteria, and proceed to the patient's enrolment.

The Investigator will record the necessary study data in the e-CRF (socio-demographics, baseline medical data). A Clinical Research Associate will help the parent download the NursTrial® App on their smartphone and create their personal access. Then, the parent will complete the study questionnaires in the App.

Study follow-up

The patient's follow-up will last as long as he/she receives Petit Drill but will not exceed 3 days and 3 nights. Indeed, to stay close to real-word condition of use of Petit Drill, the treatment duration is recommended as per IFU but not imposed in the present clinical investigation. However, the parent must specify reason for stopping the treatment in the App.

During the follow-up, the patient’s parent will have to complete the daily questionnaire and record Petit Drill intake in the App. Parents will be asked to inform the investigator of any adverse event as soon as possible.

6.11 Monitoring plan

Since this study has a patient-driven mode of data collection via a mobile application, no monitoring procedures are applicable in this case. Monitoring may not even be necessary at the patient enrolment stage in CEN Experimental, as the investigator will fill in the eCRFs without access to any source documents.

Nevertheless, alternative quality control measures can be implemented in the eCRFs and mobile application, such as field checks, predefined data entry rules to prevent incorrect or missing data entry. Simple instructions and prompts for each form or field can guide the parents and the investigators in filling the forms as accurately as possible.

Signature of the informed consent will be automatically monitored via the electronic process.

7 STATISTICAL CONSIDERATIONS

7.1 Analysis population

The analysis population will be those patients who have been included in this clinical investigation after fulfilling all selection criteria, and whose parent(s) or legal guardian did not withdraw their consent at any time (Full Analysis Set - FAS).

The analysis population is estimated to be at around 245 patients. Patient characteristics data (sociodemographic and medical) at baseline will be obtained from the analysis population (FAS).

The safety population will be made up of all patients who have used Petit Drill at least once.

The performance population will be made up of all patients for whom at least one evaluation of the primary outcome is available.

7.2 Statistical Design and Analytical Methods

The statistical analysis will be conducted in accordance with the protocol, and the Statistical Analysis Plan (SAP) which will precisely indicate the calculation of the variables, the populations studied (all, performance and safety), descriptive statistics, safety, handling of missing data. The SAP will be written as a separate document and approved prior to data review.

Statistical analyses will be performed using SAS® software (version 9.4, SAS Institute, North Carolina USA).

Since this is a purely descriptive investigation with no hypothesis, analyses of all outcomes will be performed using descriptive statistics, and no statistical tests are planned. Summary statistics will be produced for all study variables.

Continuous variables will be described by the mean, standard deviation (SD), median and range and quartile (Q1 and Q3). Some continuous variables may be converted to categorical variables, for which the numbers and increments may be defined in a more detailed statistical analysis plan (SAP). Categorical and ordinal variables will be described by the number and percentage of patients in each category, and the number and percentage of patients with missing information.

Confidence intervals of 95% will be calculated for the primary outcome and the safety secondary outcomes.

7.3 Level of significance and power

Not applicable as this is a descriptive investigation.

7.4 Determination of Sample Size

The sample size was estimated based on the worst-case scenario of the primary outcome (percentage of patients with a cough symptom score of 1 or 0 at the third night of treatment with Petit Drill® Syrup).

A total of 196 patients would provide the necessary precision of 7% of the confidence intervals (CI) for primary outcome in the most statistically unfavorable scenario (performance outcome of 50%), given

that currently available publications cannot allow for an accurate estimate of the expected primary outcome for one device.
In a previous observational study [1], a drop-out rate of 27% was observed in a cohort of children from 1 to 3 years of age, with a longer follow-up period and uncertainty regarding the mode of administration of patient questionnaires, which may suggest a slight overestimation in the context of this clinical investigation.

Due to feasibility concerns and a shorter follow-up period of 3 days, the proposed sample size is 245 patients, based on a 20% dropout rate.

7.5 Pass/fail criteria

Not applicable.

7.6 Interim analyses

No interim analyses are planned.

7.7 Criteria for the termination of the clinical investigation (if applicable)

Not applicable. Nevertheless, patients will not be prevented from withdrawing their consent to participate at any point of their participation in the investigation, and all data collection will be stopped immediately.

7.8 Management of biases

No statistical management of biases is planned, except for "missing data":

In case of missing data or loss to follow-up, sensitivity analyses could be carried out to estimate the impact of missing data on the primary outcome.

7.9 Deviations from the original statistical analysis plan

Any deviation(s) from the statistical plan during the analysis will be discussed in the final clinical investigation report (CIR).
Procedures for dealing with deviations from the original analysis plan will also be elaborated in the SAP.

7.10 Subgroups

Patients aged 6 months to 24 months old.
Patients aged 25 months old to 6 years old.

7.11 Handling of missing data and drop-outs

No imputation of missing data is planned.
In case of a considerable proportion of missing data for key outcomes (such as the primary performance outcome), sensitivity analyses will be performed. Characteristics of patients with missing and non-missing data for key variables will also be described.

7.12 Exploratory analyses

None anticipated.

7.13 Number of subjects in each pre-screening centre

Around 125 pharmacies have been proposed for patient pre-screening over a period of 6 to 9 months (at least Nov 2023 to July 2024). Given that 245 patients are planned to be recruited, this gives a mean of 2 patients per pharmacy.

8 DATA MANAGEMENT

A data management plan will be prepared and validated before data collection can begin. It will describe all functions, processes, and specifications for data collection, cleaning, and validation. This will ensure that the data are as clean and accurate as possible when presented for analysis. In addition, data collection and validation procedures will be detailed in appropriate operational documents.

8.1 Data recording

8.1.1 Case Report Forms

An eCRF will be maintained for each enrolled participant after they pass the screening stage. eCRFs will be filled by the Investigator of CEN Expérimental at the time of patient inclusion, where they will record patient sociodemographic and baseline medical data. Each patient will be pseudo-anonymized and will only be identifiable via an automatically generated unique patient ID number. Only the investigation team of CEN Expérimental or suitably trained designee will be authorized for data entry into the eCRF.

All eCRFs will be approved with an electronic signature to acknowledge/approve the data entered.

8.1.2 Mobile application

Patients' parents will record daily Petit Drill intake, respond to PROs and notify the occurrence of AEs via a mobile application over a period of 3 days from the time of inclusion. Instructions and prompts will be programmed into the mobile application to help the patients' parents with filling the form.

8.1.3 Specification of source documents

Since Petit Drill® Syrup is an OTC medication that can be purchased from the pharmacy without a prescription, the patient will not be managed in a medicalized setting. Therefore, no source documents will be available or required. Baseline data will be recorded by Investigator of CEN Expérimental via interviews with the patients' parents and legal guardians.

8.2 Data Management System

8.2.1 Procedures for data review, database cleaning and data queries.

Data collection in this study is patient-driven and via a mobile application. As a result, there will be limited potential for rectifying data entry errors at a later stage as all patient-reported data will be locked after study end. Therefore, quality control measures will be programmed in the mobile application, such as field checks and predefined data entry rules to prevent incorrect or missing data entry.
Simple instructions and prompts for each form or field will guide the parents in filling the forms as accurately as possible.

eCRFs will be managed by the investigators at CEN and similar verification features will be implemented in the eCRF to prevent incorrect data entry by the user. Based on the automatically generated queries, the data manager of CEN will be able to review and answer the found discrepancies directly in the system. All changes of data entered in the eCRF can be followed by an audit trail. A final quality control will be performed before the database is closed.

8.2.2 Procedures for data entry, verification, validation

Verification, validation and securing procedures of electronic clinical data systems will be implemented and documented by the provider of data capture systems to ensure authenticity, accuracy, reliability, and consistent intended performance of the data system from design until decommissioning of the system.

8.2.3 Database locking and storage

Statistical processing will only take place once the database has been locked, i.e., after the totality of the data has been validated and a final quality control has been performed according to the Data Validation Plan, documented by CEN. Once the data have been validated, the database will be transferred to the statistical department mandated by the sponsor for analysis.

8.2.4 Confidentiality and data protection

All personal and medical data will be pseudo-anonymized (data recorded in the pre-screen log will not contain identifying information, and collected after oral agreement of the parent). Pierre Fabre is the sole Sponsor of the study. The sponsor of the study and data controller are responsible for the processing of personal data following the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons concerning the processing of personal data and the free movement of such data (GDPR – General Data Protection Regulation) and national provision (“Reference Methodology" MR-001), the data collected being for research purposes in the field of health, the legal basis of the processing being the legitimate interest of the data controller.

Confidentiality of subject records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual subjects. At no time during the study the sponsor nor the employees of the CRO (Clinical Research Organization) CEN not involved in the investigation tasks (i.e., datamanager, statisticians, project manager, medical writer) will receive subjects identifying information. In order to maintain subject confidentiality, each subject will be assigned a unique subject identifier upon study enrolment. This subject identifier will be used in place of the subject name for the purpose of data analysis and reporting. All parties will ensure protection of subject personal data and will not include subject names or other identifiers (i.e., initials, full date of birth, address etc.) on any study forms, reports, publications or in any other disclosures, except where required by law.

8.2.5 Procedures for data retention

The Investigator must agree to preserve the following documents: the identification log of all participating subjects, a screening log, electronic copy of the eCRF, including the electronically signed and dated informed consents, the audit trail and detailed records to enable evaluations or audits from regulatory authorities, the sponsor or its designees.

These documents will be kept for all participants for a period of time specified by local regulations or specified in the Clinical Investigation Site Agreement between the investigator at CEN and the sponsor. No data should be destroyed without agreement with the sponsor.

The sponsor will maintain all documentation pertaining to this clinical investigation for the lifetime of the product. The sponsor and investigators shall take measures to prevent accidental or premature destruction of these documents and they may rely on a third party for document retention. In this case the final location and transfer procedures have to be documented.

9 AMENDMENTS TO THE CLINICAL INVESTIGATION PLAN

Any amendment to this Clinical Investigation Plan (CIP) must be approved by the sponsor and the coordinating investigator (if applicable)/or scientific committee (if applicable). When applicable, the amendment, including supporting justifications will be submitted for approval to appropriate Ethic Committee (EC) and regulatory authorities before being implemented by investigators. Furthermore, investigators will sign any amendment to indicate their agreement. It will be the responsibility of the Investigator to update study subject to new amendments that might affect willingness to continue in the study. This must be recorded in participating subject's medical file. CIP amendment approval and approval of any associated changes to the ICF must be obtained prior to implementation of the CIP amendment except when necessary to eliminate an apparently immediate hazard to participating subjects or when the change involves purely administrative or logistical aspects of the study.

10 DEVIATIONS FROM THE CLINICAL INVESTIGATION PLAN

Since this is a post-marketing clinical follow-up observational study, based in a real-life setting, no major deviations from the CIP are expected.

11 DEVICE ACCOUNTABILITY

Not applicable, as the product is commercialized (per Annexe I, clause 7 d) 1) of the EN ISO 14155 2020).

The investigator must ensure that the patients' parents or legal guardians understand the objectives of this investigation and the ICF before signing it and that they understand that the device can only be used in the patient who has been enrolled in the investigation.

In the event of a device deficiency or an adverse device effect, all details will be recorded by the parent/legal guardian in the mobile application, after which a notification will be sent to the Investigator and the data service provider (CEN). Contact will be established with the user as soon as possible by the Investigator, who will confirm the event details.

12 STATEMENTS OF COMPLIANCE

12.1 General statements of compliance

The current versions of the Guidelines of the World Medical Association's Declaration of Helsinki, EN ISO 14155 standard as well as demands of the national and European medical product laws and data protection laws (such as the GDPR) will be implemented and followed.
Compliance with these standards will ensure that the rights, safety and well-being of study subjects are protected and that data from the clinical investigation are of the highest quality standards.

All clinical work conducted under this protocol will be subject to GCP (Good Clinical Practice). The Investigator must agree to the inspection of investigation-related documents and records by health authorities, auditors and/or the sponsor or its designee upon request.

In accordance with national provisions, the start of the investigation is notified immediately (i.e. as soon as the sponsor or his representative in charge of the clinical investigation becomes aware of it) to the CPP and ANSM (*Agence Nationale de sécurité du medicament et des produits de santé)* by email until EUDAMED is made available. The effective date of the start of the clinical investigation corresponds to the date of signature of the consent form of the first person who agrees to the clinical investigation in France.
A notification of the end of the study will be sent within 15 days following the end of the clinical investigation, or its temporary interruption or its early termination to the authorities.
The summary and the clinical report will be transmitted according to the local regulation within 1 year after the end of the clinical investigation or within 3 months following the temporary interruption or early termination.
The sponsor has been informed that the competent authority (ANSM) may contact the CPP which is reviewing or which has reviewed the authorization and opinion application file for this clinical investigation.
This clinical investigation conducted under Article 82 of Regulation (EU) 2017/745 which is not subject to an insurance obligation.
The data recorded during this research is subject to computerized processing at CEN, responsible for the implementation of data processing in compliance with Regulation (EU) 2016/679 of the European Parliament and of the Council relating thereto. to the protection of individuals with regard to the processing of personal data and the free movement of such data and law n°78-17 of 6 January 1978 relating to data processing, files and freedoms, as amended by law 2018-493 of June 20, 2018.
This research is part of the "Reference Methodology" (MR-001) pursuant to the provisions of Article 54 paragraph 5 of the amended law of January 6, 1978 relating to information, files and freedoms. This change was approved by decision of January 5, 2006, updated on July 21, 2016. CEN has signed a commitment to comply with this "Reference Methodology".
The secure data collection application on smartphone NursTrial® has specific security and anonymization measures.
Pending the European database EUDAMED, this clinical investigation is registered under number ID-RCB: 2023-A01929-36.

12.2 Ethics and Regulatory Authority approval

Prior to study initiation, the CIP, sample ICF and the data collection tools will be submitted to the National Ethics Committee (Comité de Protection des Personnes – CPP – in France) for review and approval and the national competent authority (ANSM) for approval of the submitted file.

The clinical investigation will not begin until all necessary approvals/favourable opinions are obtained from the CPP and the regulatory authorities. Should the CPP and authorities impose any additional requirements, they will be duly implemented.
The sponsor and/or designee will keep on file records of approval of all documents pertaining to this study.

12.3 Financing

The costs associated with the clinical investigation and investigator/site compensation will be documented in a separate agreement that will be signed by the sponsor, the investigator and/or the management of the study site.

13 INFORMED CONSENT PROCESS

The parent(s) or legal guardian of each patient will be provided with oral (overall presentation of the study by the pharmacist) and written information in lay and native language which describes:

- The objective, nature, advantages, consequences, risks and disadvantages of the clinical investigation, the constraints, the foreseeable risks and the expected benefits of the clinical investigation;
- The rights and guarantees of the patient concerning his protection, in particular his right to refuse to participate in the clinical investigation and his right to withdraw from it at any time without incurring prejudice and without having to justify himself, and specifies the rights of the patient in the context of a clinical trial on the medical device;
- The conditions under which the clinical investigation must take place, including the planned duration of the participation of the person concerned, including the follow-up measures if the participation is terminated;
- Information relating to the identification of the clinical investigation, and the availability of results.

Each subject will be given a paper copy of the information note and of the inform consent content by the pharmacist at pre-screening step, and will encourage to carefully read this information note prior the remote visit with the Investigator.
In this clinical investigation conducted in young children, to comply with the French Public Health Code regarding the assent of the children able to understand their participation to the study, a dedicated information note will be given to the parent/legal representative. The investigator will read the letter to the child if applicable.

It is the responsibility of the Investigator to explain the details of the investigation to the subject's parent(s)/legal guardian. The Investigator or the delegated doctor/health professional answers all of the questions of the patient's parent/legal representative and ensures that he/she has understood the information and explanations provided. The patient's parent/legal representative is given the necessary duration to provide their decision to participate in the clinical investigation.

If the patient's parent/legal representative agrees to participate, the Investigator and the patient's parent/legal representative proceed to the electronic signature of the informed consent (ICF).
Before any procedures related to the research, the investigator must obtain the free, informed and written consent of the patient's parent/legal representative.

Consent will be electronically signed using a solution (*DocuSign*) whose functionality meets recommended expectations of the Guidance on computerized systems and electronic data in clinical trials (EMA/INS/GCP/112288/2023). Briefly, the system will include functionality to:

- authenticate the signatory;
- ensure non-repudiation;
- ensure an unbreakable link between the electronic record and its signature;
- provide a timestamp.

In this clinical investigation, a double level of authentication will be used (personal email and phone number). Then, the patient's parent/legal representative will receive an email with a link to access to the electronic ICF and proceed to signature after confirmation of having read the ICF.
Once signed by the patient's parent/legal representative and the Investigator), both received an electronic ICF specifying date and time for signature. The Investigator will document the signature in the e-CRF, and stored the e-ICF in the dedicated study file.

In the event that an amended ICF is implemented, it must be reviewed and signed by the subject's party and the investigator in the same way as the original consent.

The subject will not be included in the investigation under any circumstance if his/her parent(s) or legal guardian did not provide their informed consent.

14 MANAGEMENT AND REPORTING OF ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

14.1 Definitions

A qualified and suitably trained medical professional will assess all declared adverse events (AE) and adverse device effects (ADE), that would be reported by the patient/parents during the 3 days of using Petit Drill.
All definitions are issued from REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, and corresponding Medical Device Coordination Group (MDCG) guidelines.

14.1.1 Adverse Event (AE) - Article 2 (57) from MDR

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

Note 1: This includes events related to the study product (including test product and/or associated products) and/or related to the procedures involved (any procedure in the clinical investigation plan).
Note 2: For users or other persons this is restricted to events related to the investigational medical device.
Note 3: An Adverse Device Effect (ADE) is an AE related to the use of the investigational medical device.

14.1.2 *Serious Adverse Events (SAE) - Article 2 (58) from MDR*

Any adverse event that led to any of the following:

(a) death,
(b) serious deterioration in the health of the subject that resulted in any of the following:
  (i) life-threatening illness or injury,
  (ii) permanent impairment of a body structure or a body function,
  (iii) hospitalisation or prolongation of patient hospitalisation,
  (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
  (v) chronic disease.
(c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

Note 1: A planned hospitalisation for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be a serious adverse event.
Note 2: This also includes device deficiencies that might have led to a SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate.

A Serious Adverse Device Effect (SADE) is an AE related to the use of an investigational medical device and leading to the situations described above for SAEs.

14.1.3 Device deficiencies (DD) - Article 2 (59)

Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

14.1.4 Incident – Article 2 (64)

Any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect.

14.1.5 Serious incident – Article 2 (65)

Any incident that directly or indirectly led, might have led or might lead to any of the following:
(a) the death of a patient, user or other person,
(b) the temporary or permanent serious deterioration of a patient's, user's or other person's state of health,
(c) a serious public health threat *i.e.* an event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time (Article 2 (66)).

14.2 Assessment of AE and SAEs

Each AE must be assessed for seriousness, causality, severity by the investigator or another suitably qualified physician in the research team who is trained in recording and reporting AEs.
The expectedness assessment will be performed by the sponsor.
The investigator and sponsor will make an assessment of seriousness (as defined above).
The investigator and sponsor will also make an assessment of the causal relationship with the study product, and/or associated products, and/or study procedures according to the following definitions:

1. **Not related**: where an event is not considered to be related to the study product and/or associated products and/or study procedures.
2. **Possibly related**: the relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
3. **Probably related:** the relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
4. **Causal relationship**: the adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
   - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
   - the event has a temporal relationship with investigational device use/application or procedures;
   - the event involves a body-site or organ that:
     - o the investigational device or procedures are applied to;
     - o the investigational device or procedures have an effect on.
   - the adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
   - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the adverse event (when clinically feasible);
   - other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
   - harm to the subject is due to error in use;

- the event depends on a false result given by the investigational device used for diagnosis when applicable.

The investigator will make an assessment of severity for each AE and this should be recorded on the eCRF according to the following categories:
- **Mild**: an event that is easily tolerated by the research participant, causing minimal discomfort and not interfering with every day activities;
- **Moderate**: an event that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe**: an event that prevents normal everyday activities.

The term 'severe' used to describe the intensity of an event should not be confused with the term 'serious', which is a regulatory definition based on trial participant/event outcome action criteria. For example, a headache may be severe but not serious, while a minor stroke may be serious but is not severe.

14.3 Reporting of medical device cases

All AEs and DD that would occur during the 3-day follow-up period will be asked to be reported by the parents/guardians via the mobile application daily, whether they think it is related to the investigational device or not. The questionnaire to be used by the parents/guardians is provided in Table 3 above.
The questionnaire will be formulated such that the parents/guardians will be able to describe the AE to allow the determination of seriousness and causality by the investigator.
Following a declaration, an automatic notification will be sent to the investigator who will then be required to follow-up on the event.

The following would be defined as elements that could be a potential AE during the 3-day follow-up:
- Any new illness or symptom (diagnosed or undiagnosed);
- Any worsening of an existing illness or symptoms (diagnosed or undiagnosed);
- Any usual or unusual health-related event (such as loss of appetite, teething pain, reflux etc.).

Investigator's responsibility:

All these foreseeable events can be mitigated by carefully reading the IFU and by storing the device out of the reach of children and in suitable conditions as detailed in the IFU.

All AE, SAE and DD observed during the study must be reported in the eCRF by the investigator. Each AE must be assessed for seriousness, severity and causality by the investigator.

For AE or SAE including DD whether or not considered as related to the device or to the procedure the investigator will complete immediately and within 3 calendar days the form (FORM_CVI_6585) "Solicited adverse event collection form" and collect the results of the carried-out examinations and the reports of hospitalisation if applicable.
In case the investigator is aware of any new information, it should be reported to the sponsor.

Contractor's responsibility:
The contractor conducting the study will be required to provide the following information that has been brought to his attention about the investigational device within 1 business day after its acknowledgment in the eCRF:
- Any AE or SAE including DD which arises from the use of Petit Drill;
- Any SAE considered as related to the procedure of the study.

The safety information will be communicated to Pierre Fabre Vigilance department no later than 24 hours upon its reception by the contractor, through the form (FORM_CVI_6585) “Solicited adverse event collection form”, which will be sent by email: HQ.pharmacovigilance@pierre-fabre.com.

After completion of the study, newly occurring AEs potentially related to a Pierre Fabre product should be reported as spontaneous reports to the Pierre Fabre local vigilance department; a corresponding reporting form can be requested via the above contact data.

14.4 Sponsor’s responsibilities for safety reporting purposes

Sponsor or delegate will submit expedited reports to both Competent Authorities and Ethics Committees per MDR (EU) 2017/745, vigilance provisions (Articles 87-90) post-market clinical follow-up (PMCF) requirements (Article 80(5)) and the acts adopted pursuant to Article 91 of the Regulation as well as Article 80(6) where a causal relationship to the preceding investigational procedure and SAE has been established.
Article 87 – Manufacturer will notify the competent authority of the Member State in which the incident occurred according to the following timelines in the case of:

- Serious public health threat: immediately (without any unjustified delay), but not later than 2 calendar days after sponsor was informed of the threat;
- Death or any unanticipated serious deterioration in a person's state of health: immediately but not later than 10 calendar days after sponsor became aware of the event;
- Any other reportable incident: immediately but not later than 15 calendar days after sponsor became aware of the event;
- Field safety corrective actions: in advance of the action being undertaken, except in cases of urgency.

Note: Field safety corrective action’ means corrective action taken by a manufacturer for technical or medical reasons to prevent or reduce the risk of a serious incident in relation to a device made available on the market.

In line with the regulations within Regulation (EU) 2017/745 (MDR Article 80) and according to the guidance provided by MDCG-2020-10-1, the sponsor will inform all of the competent authorities of the countries in which the clinical investigation is being conducted via the summary reporting tab:

- immediately, but no later than 2 calendar days, of all SAE related to the study procedure leading to a Subject’s death, or to a life-threatening situation, serious injury or serious deterioration in Subject's health;
- immediately, but not later than 7 calendar days following the date of awareness by the sponsor of all SAE related to the study procedure leading to any other reportable events or new information in relation with an already reported event.

Sponsor or delegate will submit to all investigators information that may affect the safety of persons undergoing research.

15 VULNERABLE POPULATION

The investigational device, Petit Drill® Syrup is only intended to be used in a population that are designated as a vulnerable population: pediatric patients between 6 months and 6 years of age, who are unable to freely give their consent. All procedures pertaining to their handling and treatment have already been detailed in the above sections. There is no additional information to provide in this section.

16 SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

16.1 Definitions

Suspension: a temporary postponement of activities relating to enrollment.
Termination: a full stop of a site's study activity.

16.2 Criteria for suspension or early termination

Suspension or termination of a site may include but is not limited to:

EC approval expiration;
Consistent non-compliance to the CIP;
Lack of enrollment;
Non-compliance to regulations and the terms of the agreement with *Pierre Fabre Médicament;*
EC suspension of the product.

Consideration of suspension may include but is not limited to:

If *Pierre Fabre Médicament* decides to terminate or suspend the investigation: *Pierre Fabre Médicament* will promptly inform the site of the termination/suspension along with the reason and inform regulatory authorities, where required:

- In the case of termination or suspension for reasons other than a temporary EC approval lapse, the site will promptly inform the Ethics Committee, if applicable;
- In case of site termination, the site must inform the subjects

If the site terminates or suspends participation without prior agreement of Pierre Fabre Médicament:

The site must promptly inform *Pierre Fabre Médicament* and provide a detailed written explanation of the termination or suspension, who must then inform the EC, if applicable.

If the EC terminates or suspends its approval:

The site must promptly inform the sponsor and provide a detailed written, explanation of the termination or suspension within 5 business days;
Subject enrolment must stop until the EC suspension is lifted;
Subjects already enrolled should continue to be followed in accordance with the EC's policy or its determination that an overriding safety concern or ethical issue is involved;
The site must inform his/her institution (where required per local requirements).

17 PUBLICATION POLICY

The sponsor reserves the right to publish and present the results of this investigation at scientific meetings or to submit these data to national and international regulatory authorities.

The sponsor recognizes the right and interest of all participating investigators to scientifically publish the results obtained from this investigation for non-commercial purposes, even if the effects ascribed to the investigational device fail to materialize. Prior to any publication or presentation of results, the participating investigators will submit a draft of the intended publication or presentation to the sponsor for review and approval. For this purpose, the sponsor will be provided with a final draft in good time to allow review and comment, prior to submission (as a manuscript or abstract) or presentation. The sponsor's proposals for modifications will be taken into consideration by the participating investigators if such proposals do not interfere with the scientific nature and content of the publication.

Any publication shall suitably address contributions of co-authors. Contributors will be eligible for authorship only if they fulfil the International Committee of Medical Journal Editors (ICMJE) criteria for authorship [16].

The sponsor may request that the publication or presentation be postponed for no more than 2 months to exercise patent, copyright, or related rights. Sponsor and investigators should intend to compile a comprehensive publication of the investigation's results from all participating centers. If such a joint publication is not achieved within 2 years after the end of the study, all participating investigators shall have the right to publish the individual results from their site.

Publications from single investigational sites must make clear reference to the overall clinical investigation or CIP. The obligation to submit manuscripts for review and comment shall apply; accordingly, submissions must be made both to the sponsor and the coordinating investigator.
The identity of the sponsor and the nature of his/her contribution to the investigation is to be disclosed in any publication or presentation relating to it.

18 ANNEX

18.1 ANNEX I: IFU

335141_Notice_Petit Drill_FR_signed.pdf

18.2 ANNEX II: DT-034-PFM-520-01 Product risk management

DT-034-PFM-520-01 Annex_Product risk

18.3 ANNEX III: PCQ

The five-Item pediatric cough questionnaire

Q1. How frequent was your child's cough last night?

☐ Extremely ☐ Very much ☐ Somewhat ☐ A little ☐ Occasionally ☐ Not at all

Q2. How much did last night's cough affect your child's ability to sleep?

☐ Extremely ☐ Very much ☐ Somewhat ☐ A little ☐ Occasionally ☐ Not at all

Q3. How much did last night's cough affect your ability to sleep?

☐ Extremely ☐ Very much ☐ Somewhat ☐ A little ☐ Occasionally ☐ Not at all

Q4. How severe was your child's cough last night?

☐ Extremely ☐ Very much ☐ Somewhat ☐ A little ☐ Occasionally ☐ Not at all

Q5. How bothersome was last night's cough to your child?

☐ Extremely ☐ Very much ☐ Somewhat ☐ A little ☐ Occasionally ☐ Not at all

18.4 ANNEX IV: PAC-QoL

Q1- Were you worried/concerned about your child's cough becoming worse?

- ☐ very, very worried and concerned
- ☐ very, worried and concerned
- ☐ fairly, worried and concerned
- ☐ somewhat worried and concerned
- ☐ a little worried and concerned
- ☐ hardly worried and concerned
- ☐ not worried and concerned

Q2- Did you feel tired or exhausted because of your child's cough?

- ☐ all the time
- ☐ most of the time
- ☐ quite often
- ☐ some of the time
- ☐ once in a while
- ☐ hardly any of the time
- ☐ none of the time

Q3- Were you worried/concerned about the effects of your child's cough on him/her?

- ☐ very, very worried and concerned
- ☐ very, worried and concerned
- ☐ fairly, worried and concerned
- ☐ somewhat worried and concerned
- ☐ a little worried and concerned
- ☐ hardly worried and concerned
- ☐ not worried and concerned

Q4- Were you worried/concerned about the cause of your child's cough?

- ☐ very, very worried and concerned
- ☐ very, worried and concerned
- ☐ fairly, worried and concerned
- ☐ somewhat worried and concerned
- ☐ a little worried and concerned
- ☐ hardly worried and concerned
- ☐ not worried and concerned

Q5- Were you worried/concerned about your child not sleeping well because of the cough?

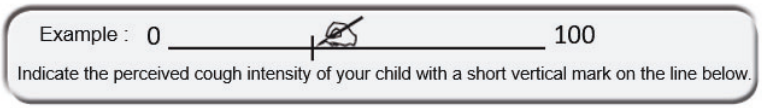
- ☐ very, very worried and concerned
- ☐ very, worried and concerned
- ☐ fairly, worried and concerned
- ☐ somewhat worried and concerned
- ☐ a little worried and concerned
- ☐ hardly worried and concerned
- ☐ not worried and concerned

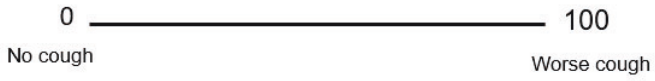
Q6- Did your family need to change plans because of your child's cough?

- ☐ all the time
- ☐ most of the time
- ☐ quite often
- ☐ some of the time
- ☐ once in a while
- ☐ hardly any of the time
- ☐ none of the time

18.5 ANNEX V: VAS

Yesterday, how was the cough of my child during the day?"





19 BIBLIOGRAPHY

1. Allaert, F.A., et al., *Observational study on the dispensing of cough syrups to children with acute cough by community pharmacists in France.* Minerva Pediatr, 2018. **70**(2): p. 117-126.
2. Koo, H.K., et al., *Development and validation of the COugh Assessment Test (COAT).* Respirology, 2019. **24**(6): p. 551-557.
3. Roy, N., et al., *An evaluation of the effects of three laryngeal lubricants on phonation threshold pressure (PTP).* J Voice, 2003. **17**(3): p. 331-42.
4. Eccles, R. and P. Mallefet, *Soothing Properties of Glycerol in Cough Syrups for Acute Cough Due to Common Cold.* Pharmacy (Basel), 2017. **5**(1).
5. Deichmann, W., *Glycerol:—Behavior in the Animal Organism—(A Review of the Literature).* American Industrial Hygiene Association Quarterly, 1940. **1**(4): p. 60-67.
6. Eccles, R., *The powerful placebo in cough studies?* Pulm Pharmacol Ther, 2002. **15**(3): p. 303-8.
7. Gray, B.A.A.B.R.E.G., *Minor Illness or Major Disease*. 5th ed. 2012, London: Pharmaceutical Press and Royal Pharmaceutical Society of Great Britain.
8. Parihar, M., et al., *A review: cough and treatments.* 2011. **1**(1): p. 9-18.
9. World Health, O., *Cough and cold remedies for the treatment of acute respiratory infections in young children*. 2001, World Health Organization: Geneva.
10. Morice, A.H., *Developing antitussives the clinician's pipeline-what do we need?* J Thorac Dis, 2014. **6**(Suppl 7): p. S735-8.
11. FDA. *Should You Give Kids Medicine for Coughs and Colds?* 2021 [cited 2022 12/09/2022]; Available from: https://www.fda.gov/consumers/consumer-updates/should-you-give-kids-medicine-coughs-and-colds.
12. Kigen, G., et al., *A Review of the Ingredients Contained in Over the Counter (OTC) Cough Syrup Formulations in Kenya. Are They Harmful to Infants?* PLoS One, 2015. **10**(11): p. e0142092.
13. MHRA. *Q&A for children's cough and cold medicines.* 2009 [cited 2022 12/09/2022]; Available from: http://www.mhra.gov.uk/home/groups/commspo/documents/websiteresources/con038905.pdf.
14. Marseglia, G.L., et al., *Acute cough in children and adolescents: A systematic review and a practical algorithm by the Italian Society of Pediatric Allergy and Immunology.* Allergol Immunopathol (Madr), 2021. **49**(2): p. 155-169.
15. Jackowska, T., et al., *PIH26 - European Study on Acute Cough in Children: Results of Poland.* Value in Health, 2017. **20**(9): p. A524.
16. ICMJE. *Defining the Role of Authors and Contributors*. 2021 [cited 2021 02-December-2021]; Available from: http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html.
17. Hartnick CJ, Zurakowski D, Haver K. Validation of a pediatric cough questionnaire. *Ear Nose Throat J*. 2009;88(11):1213-1217.
18. Anderson-James S, Newcombe PA, Marchant JM, et al. An acute cough-specific quality-of-life questionnaire for children: Development and validation. *J Allergy Clin Immunol*. 2015;135(5):1179-1185.e1-4. doi:10.1016/j.jaci.2014.08.036
19. Anderson-James S, Newcombe PA, Marchant JM, Turner CT, Chang AB. Children's Acute Cough-Specific Quality of Life: Revalidation and Development of a Short Form. *Lung*. 2021;199(5):527-534. doi:10.1007/s00408-021-00482-2
20. Lee KK, Matos S, Evans DH, White P, Pavord ID, Birring SS. A longitudinal assessment of acute cough. *Am J Respir Crit Care Med*. 2013;187(9):991-997. doi:10.1164/rccm.201209-1686OC
21. Byrom B, Elash CA, Eremenco S, et al. Measurement Comparability of Electronic and Paper Administration of Visual Analogue Scales: A Review of Published Studies. *Ther Innov Regul Sci*. 2022;56(3):394-404. doi:10.1007/s43441-022-00376-2

19.1 Guides and standards for the preparation of the CIP

1. The Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

2. The EN ISO 14155-2020 standard for Clinical investigation of medical devices for human subjects - Good Clinical Practice

3. MDCG 2020-10/1 Rev 1 Guide on Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745

4. MDCG 2020-6 Guide on Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC

5. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)

6. Law n°78-17 of 6 January 1978 relating to data processing, files and freedoms, as amended by law 2018-493 of June 20, 2018

SIGNATURE PAGE

The signatures of the sponsor and coordinating investigator(s), or any other relevant third party (such as a CRO representative) indicating their agreement with the contents of the report, should be provided. If no coordinating investigator is appointed, then the signature of the principal investigators should be obtained. The signature pages may be separate from the clinical investigation report itself.

The undersigned declare that they agree with the contents of this Clinical Investigation Plan.

Signatures Name and Responsibility*	Date	Signature
Pierre Fabre Representative 1 **Eric GARRIGUE** **Pierre Fabre** **Global Medical Director**	26-juin-2024 | 23:16 CEST	DocuSigned by: Didier Junquero Nom du signataire : Didier Junquero Motif de la signature : J'approuve ce document Heure de signature : 26-juin-2024 | 23:15 CEST
Pierre Fabre Representative 2 **Farida BEGHDAD** **Pierre Fabre** **RWE Project Leader**	27-juin-2024 | 15:16 CEST	DocuSigned by: [illegible]1F99513AFC7AFAC41B3 Nom du signataire : Abir TADMOURI Motif de la signature : J'approuve ce document Heure de signature : 27-juin-2024 | 15:16 CEST
Scientific Committee Representative 1 **Docteur Vincent ALQUIER** **Coordinating Pharmacist**	27-juin-2024 | 10:28 CEST	DocuSigned by: 633B01244AA6445D93C0568AA5E09AF8 Nom du signataire : Vincent ALQUIER Motif de la signature : J'approuve ce document Heure de signature : 25-juin-2024 | 21:06 CEST
Scientific Committee Representative 2 **Professeur Guy DUTAU**	25-juin-2024 | 13:44 CEST	DocuSigned by: CD[illegible]29F40BFAFB13BD5618EB3C1 Nom du signataire : Guy Dutau Motif de la signature : J'approuve ce document Heure de signature : 25-juin-2024 | 13:44 CEST
CRO Representative **Georges MAYEUX** **CEN DIRECTOR**	25-juin-2024 | 14:28 CEST	DocuSigned by: BF981A7A3CA841C79A7C8315BCEEC7E7 Nom du signataire : Georges Mayeux Motif de la signature : J'approuve ce document Heure de signature : 25-juin-2024 | 14:28 CEST
Coordinating Investigator 1 **Myriam SIMIAN** **CEN EXPERIMENTAL**	27-juin-2024 | 14:08 CEST	DocuSigned by: [illegible]274B1698F0C7881AFF19C1 Nom du signataire : Myriam SIMIAN Motif de la signature : J'approuve ce document Heure de signature : 27-juin-2024 | 14:08 CEST

I agree to conduct the study in accordance with the current Clinical Investigation Plan.

Principal Investigator's Name (print)	
Principal Investigator's Signature	
Date	

Please retain the signed original of this form in your study files. Please return a copy of this signed original form as instructed by Pierre Fabre Médicament.

DocuSign

Certificat de réalisation

Identifiant d'enveloppe: 03125905517448D0A3702413DAC1B453

État: Complétée

Objet: Complétez l'enveloppe avec Docusign : C1735_PROTOCOLE_6.0_AEFY_20240326.pdf

Enveloppe source:

Nombre de pages du document: 65

Signatures: 6

Émetteur de l'enveloppe:
Amandine FRY
18 Rue Pauline Kergomard
DIJON, FR 21000
amandine.fry@groupecen.com
Adresse IP: 212.234.11.105

Nombre de pages du certificat: 7

Paraphe: 0

Signature dirigée: Activé

Horodatage de l'enveloppe: Désactivé

Fuseau horaire: (UTC+01:00) Bruxelles, Copenhague, Madrid, Paris

Suivi du dossier

État: Original
25/06/2024 12:34:02

Titulaire: Amandine FRY
amandine.fry@groupecen.com

Emplacement: DocuSign

Événements de signataire	Signature	Horodatage
Abir TADMOURI abir.tadmouri.sellier@pierre-fabre.com RWE & Data Director Pierre Fabre Niveau de sécurité: E-mail, Authentification de compte (obligatoire)	Abir TADMOURI Sélection d'une signature : Style présélectionné ID de signature: 633B0124-4AA6-445D-93C0-568AA5E09AF8 En utilisant l'adresse IP: 213.190.76.192 Avec authentification de signature via mot de passe DocuSign Avec motifs de signature (sur chaque onglet): J'approuve ce document	Envoyée: 25/06/2024 12:44:30 Renvoyé: 25/06/2024 15:58:30 Consultée: 27/06/2024 15:15:53 Signée: 27/06/2024 15:16:36

Divulgation relative aux Signatures et aux Dossiers électroniques:
Accepté: 27/06/2024 15:15:53
ID: a66d327b-e73a-4971-a324-bab6be0d91e1

Didier Junquero didier.junquero@pierre-fabre.com Corporate Medical Advisor, Pharmaceutical Care Pierre Fabre Médicament Niveau de sécurité: E-mail, Authentification de compte (obligatoire), Connexion avec SSO	Didier Junquero Sélection d'une signature : Style présélectionné ID de signature: 280A3718-0FBB-41F9-9513-AFC7AFAC41B3 En utilisant l'adresse IP: 213.190.76.192 Avec authentification de signature via mot de passe DocuSign Avec motifs de signature (sur chaque onglet): J'approuve ce document	Envoyée: 25/06/2024 12:44:29 Consultée: 26/06/2024 23:14:52 Signée: 26/06/2024 23:16:05

Divulgation relative aux Signatures et aux Dossiers électroniques:
Accepté: 26/06/2024 23:14:52
ID: b5917444-26fb-4e66-b626-eeb24382a969

Événements de signataire	Signature	Horodatage
Georges Mayeux georges.mayeux@groupecen.com Gérant CEN Niveau de sécurité: E-mail, Authentification de compte (obligatoire)	 Sélection d'une signature : Style présélectionné ID de signature: 91E2C2D3-1527-4B16-98F0-C7881AFF19C1 En utilisant l'adresse IP: 212.234.11.105 Avec authentification de signature via mot de passe DocuSign Avec motifs de signature (sur chaque onglet): J'approuve ce document	Envoyée: 25/06/2024 12:44:31 Consultée: 25/06/2024 14:28:06 Signée: 25/06/2024 14:28:30
Divulgation relative aux Signatures et aux Dossiers électroniques: Non offerte par DocuSign		
Guy Dutau guy.dutau@wanadoo.fr Niveau de sécurité: E-mail, Authentification de compte (obligatoire)	 Sélection d'une signature : Style présélectionné ID de signature: BF981A7A-3CA8-41C7-9A7C-8315BCEEC7E7 En utilisant l'adresse IP: 90.89.185.180 Avec authentification de signature via mot de passe DocuSign Avec motifs de signature (sur chaque onglet): J'approuve ce document	Envoyée: 25/06/2024 12:44:31 Consultée: 25/06/2024 13:43:38 Signée: 25/06/2024 13:44:39
Divulgation relative aux Signatures et aux Dossiers électroniques: Accepté: 25/06/2024 13:43:38 ID: 5ff1b761-d8b8-4e07-bf2d-bdc099981e9f		
Myriam SIMIAN simian.myriam@gmail.com Niveau de sécurité: E-mail, Authentification de compte (obligatoire)	 Sélection d'une signature : Style présélectionné ID de signature: 8F156853-0FA0-439D-9BA5-975F5B0CDF73 En utilisant l'adresse IP: 212.234.11.105 Signé à l'aide d'un périphérique mobile Avec authentification de signature via mot de passe DocuSign Avec motifs de signature (sur chaque onglet): J'approuve ce document	Envoyée: 25/06/2024 12:44:31 Consultée: 27/06/2024 14:07:58 Signée: 27/06/2024 14:08:34
Divulgation relative aux Signatures et aux Dossiers électroniques: Accepté: 27/05/2024 18:39:33 ID: 62cf4c10-655a-4f77-ad4f-644f51b4d399		

Événements de signataire	Signature	Horodatage
Vincent ALQUIER vincentalquier2905@gmail.com Pharmacien titulaire Niveau de sécurité: E-mail, Authentification de compte (obligatoire)	 Sélection d'une signature : Écrit sur un appareil ID de signature: CD8A412C-129F-40BF-AFB1-3BD5618EB3C1 En utilisant l'adresse IP: 92.184.100.28 Signé à l'aide d'un périphérique mobile Avec authentification de signature via mot de passe DocuSign Avec motifs de signature (sur chaque onglet): J'approuve ce document	Envoyée: 25/06/2024 12:44:30 Consultée: 25/06/2024 21:04:06 Signée: 27/06/2024 10:28:07

Divulgation relative aux Signatures et aux Dossiers électroniques:
Accepté: 25/06/2024 21:04:06
ID: 23ba094c-464b-4c50-86f5-c605a8632c69

Événements de signataire en personne	Signature	Horodatage

Événements de livraison à l'éditeur	État	Horodatage

Événements de livraison à l'agent	État	Horodatage

Événements de livraison intermédiaire	État	Horodatage

Événements de livraison certifiée	État	Horodatage

Événements de copie carbone	État	Horodatage
Constance BATTIN constance.battin.ext@pierre-fabre.com Niveau de sécurité: E-mail, Authentification de compte (obligatoire)	**Copié**	Envoyée: 25/06/2024 12:44:32 Consultée: 27/06/2024 16:39:59
Pauline GOUBET pauline.goubet@groupecen.com Niveau de sécurité: E-mail, Authentification de compte (obligatoire)	**Copié**	Envoyée: 25/06/2024 12:44:33 Consultée: 28/06/2024 09:32:07

Divulgation relative aux Signatures et aux Dossiers électroniques:
Non offerte par DocuSign

Divulgation relative aux Signatures et aux Dossiers électroniques:
Accepté: 06/11/2023 12:26:44
ID: 138fe9c3-2735-4869-b4b7-be9bbde814ca

Événements de témoins	Signature	Horodatage

Événements notariaux	Signature	Horodatage

Récapitulatif des événements de l'enveloppe	État	Horodatages
Enveloppe envoyée	Haché/crypté	25/06/2024 12:44:33
Enveloppe mise à jour	Sécurité vérifiée	25/06/2024 15:58:29
Enveloppe mise à jour	Sécurité vérifiée	25/06/2024 15:58:29
Enveloppe mise à jour	Sécurité vérifiée	25/06/2024 15:58:29
Livraison certifiée	Sécurité vérifiée	25/06/2024 21:04:06

Récapitulatif des événements de l’enveloppe	**État**	**Horodatages**
Signature complétée	Sécurité vérifiée	27/06/2024 10:28:07
Complétée	Sécurité vérifiée	27/06/2024 15:16:36

Événements de paiement	**État**	**Horodatages**

Divulgation relative aux Signatures et aux Dossiers électroniques

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, CEN (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact CEN:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: arnaud.terrillon@groupecen.com

To advise CEN of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at arnaud.terrillon@groupecen.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from CEN

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to arnaud.terrillon@groupecen.com and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with CEN

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to arnaud.terrillon@groupecen.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify CEN as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by CEN during the course of your relationship with CEN.