CLINICAL STUDY PROTOCOL

Open-label, prospective study to assess the safety, tolerability, analgesic effect and feasibility of IN SUF/KET in pediatric patients with moderate or severe pain, in an acute care setting

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Investigational medicinal product: Sufentanil(citrate)/ketamine(hydrochloride) for intranasal use

Investigational medicinal product code: CT001

Development phase: 2

Coordinating Investigator:
[redacted]
Birmingham Children's Hospital
Steelhouse Lane
Birmingham B4 6NH
England

Sponsor:
Cessatech A/S
Strandvejen 60
2900 Hellerup Denmark

Contract Research Organization Europe:
SMERUD Medical Research International AS
Thunes Vei 2
N-0274 Oslo
Norway

Contact Information

Sponsor

Primary contact:
[redacted]
Cessatech A/S
Strandvejen 60
2900 Hellerup
Denmark
[redacted]
[redacted]

Medical monitor:
[redacted]
Cessatech A/S
Strandvejen 60
2900 Hellerup
Denmark

CRO

SMERUD Medical Research International AS
Thunes Vei 2
N-0274 Oslo
Norway
Tel.: +47 23 27 20 00
Fax: +47 23 27 20 01
Web: www.smerud.com

SAE reporting

E-mail: pharmacovigilance@smerud.com

TABLE OF CONTENTS

PROTOCOL OUTLINE

Title of Study & Design	**PDC 01-0202:** Open-label, prospective study to assess the safety, tolerability, analgesic effect, and feasibility of IN SUF/KET in pediatric patients with moderate or severe pain, in an acute care setting
Study population	Pediatric participants from 1 year to <18 years inclusive. The aim will be to recruit the following minimum participants per age group: Age 1 - <5 years: 20 participants Age 5 - <9 years: 40 participants Age 9 - <18 years : 40 participants The remaining participants can be flexible enrolled.
Number of patients	150 pediatric participants evaluable for the primary endpoint
Investigators/ Study Sites	The study will be conducted at multiple sites in the Europe

Diagnosis and Main Criteria for Inclusion	Key inclusion criteria:
	- Pediatric participant, age 1 year to <18 years
	- Attending an Emergency Department (ED) following an injury
	- Acute pain of moderate or severe intensity (corresponding to 5 or above on an age-appropriate pain scale (0-10 NRS, Wong-Baker FACES scale and FLACC pain scale)
	- Obtained informed consent by parent/guardian and assent from the child if possible and relevant (age dependent)
	Key exclusion criteria:
	- Participant showing abnormal nasal cavity/airway such as:
	  - major septal deviation
	  - evidence of previous nasal disease or surgery
	  - current significant nasal congestion due to common cold
	- Has received treatment with sufentanil and/or ketamine during the last 72 hours
	- Known or suspected allergy to ketamine or sufentanil
	- Critical, life- or limb-threatening condition requiring immediate management

Test Product, Dose and Mode of administration	[redacted] The dose may be repeated once after 10-15 min in case sufficient analgesia is not achieved after the first dose (i.e. pain intensity score >4/10 on age-appropriate pain scale per PI discretion).
Duration of Treatment	Patients will receive a single dose of CT001, with the option of a second dose after 10-15 min where sufficient analgesia is not achieved after first dose. Efficacy, safety monitoring, including measurement of vital signs will continue for 60 min. after the last dose or until rescue medication or procedures are initiated.
Control(s)	None

Primary Objectives	Endpoints	Assessments
To assess the safety and tolerability of CT001 in pediatric participants with moderate to severe pain in an acute care setting	The number and proportion (%) of participants with AEs Number of AEs, graded by severity, and number of SAEs.	Pulse rate, Respiratory rate Peripheral oximetry Nasal irritation: (Combined participant and investigator reported nasal symptoms will be collected from all patients) Sedation: (The University of Michigan Sedation Scale (Malviya et al, Anesthesiology 2004) Unsolicited adverse events (incl CNS AE's)
To evaluate the analgesic effect of CT001 in pediatric participants with moderate to severe pain in an acute care setting	Number and proportion (%) of participants that respond to the treatment relative to baseline (i.e. reduction in pain score to 4 or below) at 15 min post IMP administration. Number and proportion (%) of participants that respond to the treatment relative to baseline (i.e. reduction in pain score to 4 or below) within 30 min post IMP administration.	Pain intensity score: For age group ≥ 1 year to < 5 years FLACC score (assessed by site staff). For age group ≥ 5 years up to 9 years visual analogue scale modified with Wong-Baker faces For age group 9 to < 18 years Numerical Rating Scale (NRS) 0-10.

Secondary Objectives	Endpoints	Assessments
To assess medication errors in pediatric participants with moderate to severe pain in an acute care setting	Number of medication errors	Type of medication errors (will be obtained via feedback from site staff that administer the IMP)
To evaluate other analgesic effects of CT001 in pediatric participants with moderate to severe pain in an acute care setting	Maximum change from baseline in pain intensity within 30 min post IMP administration. Number and proportion of participants that achieve a 30% reduction in pain intensity relative to baseline within 30 min post IMP. Change from baseline in pain intensity at 10, 15, 20, 30, 45 and 60 min post IMP. Derived variables such as area under curve (AUC), peak change in pain intensity, and duration of effect will be calculated from the recorded pain assessments.	Pain intensity score: For age group ≥ 1 year to < 5 years FLACC score (assessed by site staff). For age group ≥ 5 years up to 9 years visual analogue scale modified with Wong-Baker faces For age group 9 to < 18 years Numerical Rating Scale (NRS) 0-10."
To evaluate the need of supplemental analgesics.	Number and proportion (%) of participants receiving additional analgesics.	Time to the need for additional analgesics (will be obtained from the entire population)
To evaluate feasibility of CT001 in pediatric participants with	Average treatment satisfaction as assessed by respondents on a 5-point Likert scale	A standardized question will be used: "*How satisfied are you with the study drug that you/your child received? Please think*

moderate to severe pain in an acute care setting		*about how it helped their pain, how it was given, any side effects, and how quickly you/your child recovered*". Respondents will answer using a 5-point Likert scale (very unsatisfied, unsatisfied, neutral, satisfied, very satisfied). Children that can orally give feedback will do so and for those that are too young, parent/guardian or site staff will provide input.
	Feasibility / Acceptance of nasal administration.	Acceptance of the intranasal route of administration by asking the child: "*If you were in this situation again and needed pain medication, would you like to receive the nasal spray*? If not possible by the child, then input will come from the parent/guardian.

Statistical Methods	General principles The primary objective of this study is to investigate the safety, tolerability and analgesic effects of CT001 in pediatric participants when used in an acute care setting. Data will be summarised using descriptive statistics. For continuous endpoints, the descriptive statistics include number of subjects, mean, median, standard deviation, standard error, lower and upper quartiles, minimum, and maximum. For categorical endpoints, frequency, and percentage will be given. Figures showing population distributions, such as box plots and histograms, will be reported for all applicable endpoints. The method of handling missing data for efficacy endpoints will be described for each set of endpoints. Missing data will not be imputed for safety endpoints. Sample size estimation So far, data from 375 children on IN sufentanil/ketamine show a safe and tolerable combination (data from PDC 01-0201, PDC 01-0203 and PDC 01-0206). Thus, from a safety perspective it is expected that 150 patients will be sufficient to capture and confirm the adverse event profile of the IMP. A formal sample size calculation was made for the primary efficacy endpoint on the basis of expecting a responder rate of 60%. A previous study reported a responder rate of 71.6 %, defined as pain intensity <= 3 at 30 min post IMP (16). With a sample of 113 patients, a one-sample one-sided proportion design would provide at least 80% power to show that the responder rate is more than to 60%, with a significance level of 5%. Accounting for an approximate 25% dropout rate the resulting sample size is 150. Study populations The full analysis set (FAS) will consist of all patients who received at least one dose of study treatment (CT001). The FAS follows the intention-to-treat (ITT) principle, i.e. patients will be analysed regardless of whether treatment was received as planned. The FAS will be used for all analyses of primary and secondary safety and efficacy objectives. The FAS will be used to tabulate demographic data, baseline disease characteristics, and subject disposition. Statistical analysis of the primary endpoints The primary objective of the study will be evaluated using the FAS population. Data will further be evaluated by age group. Descriptive statistics will be used for safety variables. Safety variables of special interest consist of vital signs, respiratory rate, pulse rate, oxygen saturation (SpO2), heart rate as well as sedation. Clinically significant out-of-range values and clinically significant relevant changes of values will be described descriptive statistics, number of subjects, number of events. Adverse events will be coded according to the MedDRA dictionary. The frequencies of adverse events will be tabulated by body system and "preferred term".

	The analgesic efficacy variable, responder rate (pain intensity of 4 or below at 15 min and within 30 min post IMP), will be reported using descriptive statistics. <u>Statistical analysis of secondary endpoints</u> All secondary endpoints will be analysed using descriptive statistics. Besides reporting summary descriptive statistics, Means and corresponding 90% symmetric confidence intervals estimated using the change from baseline in the respective variable unit.

LIST OF ABBREVIATIONS

AE	Adverse Event
AUC	Area Under Curve
CNS	Central Nervous System
CRA	Clinical Research Associate
CSR	Clinical Study Report
DM	Data Manager
DPO	Data Protection Officer
EC	Ethics Committee
ED	Emergency Department
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	The European Medicines Agency
FAS	Full Analysis Set
FLACC	Face, Legs, Activity, Cry, Consolability
GCP	Good Clinical Practice
CHMP	Committee for medicinal Products for Human Use
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IN	Intranasal
IQR	Interquartile Range
ITT	Intention-To-Treat
IV	Intravenous
KET	Ketamine
kg	kilogram
NRS	Numerical Rating Scale
mcg	microgram
min	minute
mg	milligram
mL	millilitre
PI	Principal Investigator
PIP	Pediatric Investigational Plan
PK	Pharmacokinetic
QP	Qualified Person
SAE	Serious Adverse Event
SD	Standard Deviation
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SUF	Sufentanil
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
UMSS	University of Michigan Sedation Score

1 INTRODUCTION

1.1 Background

The proposed study aims to investigate the safety, tolerability, analgesic efficacy, and feasibility of intranasal (IN) sufentanil/ketamine (CT001) in pediatric participants attending an acute care (i.e. emergency) setting. The study is a part of the clinical development plan for the development of CT001 nasal spray for treatment of acute pain in children. The pediatric investigation plan (PIP) for CT001 nasal spray has been approved by the European Medicines Agency (EMA) in November 2019 (EMA_001739-PIP02-16) (1).

1.2 Rationale for development of CT001 nasal spray

Treatment of acute and procedural pain in children is characterized by frequent off-label use of pharmaceuticals with no evidence-based effect in the pediatric population, as well as pharmaceuticals with only a sedative effect, thus leaving the pain untreated. Despite the many pain-relieving products available for adult patients, few of these have been developed for children and the treatment of acute pain in pediatric participants is characterized by a significant unmet medical need.

IN drug administration for management of acute or procedural pain has several advantages over oral, rectal, or injectable drug formulations, including needle-free administration, easy to administer, rapid onset of therapeutic effect, and direct absorption to the systemic blood supply avoiding hepatic first-pass metabolism. IN administration is also applicable in situations where intravenous (IV) access for rescue analgesic treatment is not feasible or cannot be obtained e.g., in the prehospital setting or the emergency department (ED) setting. However, in most of the published studies of IN analgesia, commercially available drug preparations were used as nasal drops or non-standardised sprays resulting in a dosing volume of up to several millilitres (mL's) (2,3) potentially resulting in the swallowing of the drug and consequently gastrointestinal adverse events. Thus, a standardised pharmaceutical formulation is needed to ensure efficacious and safe analgesic treatment in the pediatric population.

1.3 Drug Class

The active substances in CT001 are sufentanil citrate and ketamine hydrochloride, used in a fixed combination for IN use. From the Summary of Product Characteristics (SmPC), Sufentanil is authorized as a solution for IV or epidural injection (Sufenta) (4) and ketamine is authorized as a solution for injection (SmPC Ketamin Abcur) (5). However, no marketing authorization exists for the combination of sufentanil and ketamine as a nasal spray, consisting of a new pharmaceutical formulation.

Sufentanil and ketamine act at different central nervous system (CNS) sites (mu-opioid receptor agonist and N-methyl D-aspartate receptor antagonist, respectively). Sufentanil's mechanism of action is like other opioids, and it has an analgesic effect and a dose-dependent sedative effect.
Ketamine has a dose-pendent action as a general anaesthetic agent producing an anaesthetic state termed "dissociative anaesthesia" characterized by profound analgesia. Ketamine has an analgesic effect at sub-anaesthetic plasma concentrations. Psychotomimetic side effects including hallucinations, abnormal dreams, nightmares, confusion, and abnormal behaviour occur commonly (≥1/100 to <1/10 patients) with anesthetic doses of ketamine (5). However, perioperative use of injectable ketamine in children in sub-anesthetic/analgesic doses (median 0.5 mg/kg) has not been associated with psychomimetic side effects (6). The dose of ketamine in CT001 is equivalent to low analgesic doses.
The fixed combination of IN sufentanil and ketamine may provide an additive analgesic effect (also referred to as balanced analgesia). Thus, lower doses of sufentanil and ketamine may be needed to achieve adequate analgesia (relative to sufentanil alone) resulting in potentially fewer adverse events (AEs).

1.4 Previous Non-clinical and Clinical Studies

1.4.1 Non-Clinical Studies

The nonclinical profile of CT001 (fixed medicinal product containing the two active ingredients sufentanil and ketamine) is based on bibliographical research on safety and toxicity data for sufentanil, ketamine and the free combination of the two active ingredients. For further information see the current Investigator's Brochure, version 5.0.
No further non-clinical studies will be conducted as agreed at a Scientific Advice with CHMP at the European Medicines Agency (EMEA/H/SA/3623/1/2017/PED/II) and in the approved pediatric investigation plan (1).

1.4.2 Clinical studies

There is currently extensive clinical experience with both ketamine and sufentanil. Sufentanil is marketed in several EU Member States as solution for IV or epidural injection. Sufentanil was first approved in Belgium and Luxemburg in 1978 (4). Sufentanil is approved for adults and children above 1 month for maintenance of anaesthesia, for epidural analgesia in adults including epidural analgesia during labour and delivery and epidural analgesia in children above 1 year. Ketamine is marketed in several EU Member States. Ketamine was first approved by the Food and Drug Administration in 1970 as a solution for injection. Ketamine and its enantiomer s-ketamine are approved for adults and children (no age specified) for induction of anesthesia, analgesic supplement in regional and local analgesia and analgesia in acute situations. In general, IV opioids (e.g. sufentanil) and ketamine are used in combination for different analgesic regimes as ketamine has been indicated to potentiate the analgesic effect of opioids (5,7). Thus, sufficient analgesia may

be achieved with a lower dose of opioid when combined with ketamine than with opioid monotherapy, thereby reducing the risk of opioid-related adverse events, including respiratory depression.

CT001 has been investigated in several clinical studies. The doses of IN sufentanil and ketamine were based on wide clinical experience from off-label use of commercially available solutions administered as nasal drops (8,9). [redacted] Heart rate and oxygen saturation were stable, and sedation was minimal. No serious adverse events (SAEs) were reported.

Bibliographic data of IV sufentanil and ketamine has indicated that for children out of infancy (approx. >2 years) pharmacokinetics of sufentanil and ketamine are well described using allometric models. Investigation of absolute bioavailability of IN administration is challenging in the pediatric population and absolute bioavailability of the IN sufentanil/ketamine fixed combination in adults has been conducted in a separate PK bridging study (PDC01-0204) using the proposed administration device. The study included 15 healthy volunteers in a cross-over study design where 14 received intranasal 27 microg sufentanil / 27 mg ketamine, 15 subjects received 10 mg ketamine intravenously and 14 subjects received 10 microg sufentanil IV. The estimated bioavailability for sufentanil and ketamine was 39% and 47%, respectively.

For an overview of published studies of IN sufentanil and IN ketamine/s-ketamine and IN sufentanil/ketamine/s-ketamine combinations please refer to the current Investigator's Brochure, version 5, which includes data from both published studies and clinical experience of more than 700 children that have received IN sufentanil or ketamine/s-ketamine or combinations of sufentanil and ketamine/s-ketamine.

1.5 Ongoing Clinical Study with CT001

One phase II study is currently ongoing with CT001. The primary objectives for the PDC01-0205 study are to investigate the analgesic effect and the concentration-effect relationship (pharmacokinetic-pharmacodynamic relationship) across different IN doses of sufentanil, ketamine and CT001 (sufentanil/ketamine fixed combination) for the treatment of acute postoperative pain in adults undergoing removal of an impacted mandibular third molar.

1.6 Rationale of the Present Study

This open-label prospective study aims to investigate the safety, tolerability, analgesic efficacy, and feasibility of one or two repeated doses of IN sufentanil/ketamine in pediatric participants aged 1-17 years (inclusive), suffering from moderate to severe pain while being in an acute care setting.

The pharmacological rationale of the CT001 is a multimodal (balanced) analgesic treatment combining low-dose sufentanil and low-dose ketamine providing analgesic plasma concentrations with concomitant reduced risk of opioid-related side effects, including respiratory depression.

This phase II study is the last study as part of the clinical development plan for the development of sufentanil/ketamine nasal spray for treatment of acute and procedural pain in children. The pediatric investigation plan (PIP) for sufentanil/ketamine nasal spray has been approved by the European Medicines Agency in November 2019 (EMA_001739-PIP02-16) (1).

1.7 Ethical Considerations

1.7.1 Risk and inconveniences to the patients

Acute pain of moderate to severe intensity is common in children in the acute care (i.e. emergency) setting. In most cases oral treatments do not provide sufficiently rapid analgesia. Intramuscular and subcutaneous injections are also slow-acting, as well as being painful when administered. A fast titration of an effective dose within a reasonable time is also not possible. Thus, standard-of-care to date to manage acute moderate to severe pain is mainly off-label IN opioids. The IN route of administration has been well accepted in clinics and acute care settings by both children, parents, and healthcare staff due to its low invasiveness and high effectiveness.

The IMP CT001 will be administered intranasally. Both sufentanil and ketamine are well-known drugs for the treatment of acute pain (9). The doses of the IMP (CT001) have previously been shown to be effective in a clinical setting in children for procedural pain management (10).

Common dose-dependent side effects of sufentanil are nausea, vomiting, itching and sedation (1-≥10%) (4). While for IV ketamine (in sub-anesthetic doses used for analgesia), sedation and nausea/vomiting are common side effects (5). In the completed pediatric study (PDC 01-0201, EudraCT 2009-013801-33) investigating the IN combination of sufentanil and ketamine unpleasant taste, vomiting and dizziness were the most common adverse events, see Investigators Brochure, version 5.

Study medication will be administered on one occasion, with the possibility of adding a second dose if the first dose did not result in sufficient pain relief as per investigator discretion. Pain intensity will be assessed using age-relevant pain intensity scoring scales.

During and following IN administration of the combination of study drug, non-invasive assessments of heart rate, oxygen saturation and respiratory rate will be done. A physician will be present when the IMP is administered in case of potential side effects requiring any additional treatment. During the study participation, the child and parent/legal guardian will be queried for subjective adverse

events. Furthermore, the study will focus on assessment of nasal tolerability to ensure that the IMP is not associated with local irritation of the nasal mucosa. Patients will be asked specific questions related to nasal tolerability.

1.7.2 Euphoria and psychological dependency

A well-known, serious adverse effect of exposure to opioids is the potential development of addictive behaviour i.e., a biopsychosocial determined motivational phenomenon including strong and compulsive, rewarding and reinforcing experiences. Experiencing opioid-induced euphoria, even during a short-lasting exposure, unfortunately, may lead to a state of addiction and psychological dependency. Since 2016, in the context of the "opioid epidemic" in the U.S., a high prevalence of persistent post-surgical use of opioids has been identified in previous opioid-naïve patients (11–13). It is not known how much of the prevalence (3-7%) from the post-surgical population that reflects persistent post-surgical pain state or a psychological dependency.

However, continued opioid prescription for more than three months following a post-surgical scenario, cannot be rightfully extrapolated to the present experimental scenario with one or maximum two administrations, i.e., only a short exposure time to sufentanil. Consequently, the risk for patients to become dependent or experience euphoria after being part of this study is considered minimal.

1.8 Benefit-Risk Assessment

Patients who present to an ED suffering from moderate or severe acute pain following an isolated injury will be approached for recruitment. In the context of this study, an isolated injury refer to “a non-critical and non-limb threatening physical wound or injury of the tissues”, including (but not limited to) closed fractures of the extremities, joint dislocations, joint sprains, burns and scalds, soft tissue lacerations, and penetration by foreign bodies.

After obtaining informed consent from an accompanying parent/legal guardian (or from competent 16- and 17-year-old patients is accepted per local regulations) +/- assent from the child (per local regulations), the child will receive study treatment according to the study protocol. There is no placebo group in the study and the open-label study design will minimize any untoward delay in receiving acute pain relief. The patients are expected to have a direct benefit of CT001.

Standard of care for acute pain management in an emergency setting already includes IN or IV opioids. However, when used as IV injection, it requires the insertion of an IV cannula before pain treatment can be administered. This procedure may be painful and, in an emergency setting, also challenging for the nurse or doctor conducting the insertion. Current use of IN opioid administration is frequently performed using commercially available IV opioids preparations using a mucosal atomization device. This approach may require up to several milliliters of drug (depending on weight

of the child) causing possibly swallowing of the drug and consequently gastrointestinal adverse events. There is less risk of this with CT001 as the volume required will be much less (See IMP section for more details).

For the investigational product (IMP, CT001) the doses are comparable to the doses used as premedication before anesthesia in opioid-naïve patients and administration is not expected to be associated with substantial risk or unknown adverse events. Administration of opioids like sufentanil may cause mild side effects like nausea/vomiting, sedation and itching in some patients, regardless of the dose. The children and their parents/legal guardians will be well-informed (age adjusted) about receiving an opioid in this trial. The potential benefit for the pediatric population of the easy to administer, analgesic treatment, is considered to outweigh the expected low risk in these patients.

1.8.1 Pregnancy and acute opioid and ketamine use

Limited amount of data exists from the use of sufentanil and ketamine during pregnancy. Sufentanil and ketamine crosses the placenta. There are, however, no indications to date that the use of sufentanil during pregnancy increases the risk of congenital abnormalities. The risk to the fetus can depend on various factors such as the gestational age of the pregnancy, dosage and duration of sufentanil and ketamine use.

In the current study CT001 will be used for acute pain management only and the duration of sufentanil and ketamine exposure will be very limited. Known pregnancy is a protocol exclusion criterion and the site staff will ask female participants that have reached menarche if they may be pregnant (and thus excluded). For ethical reasons it is not feasible in the ED setting to perform urine or serum pregnancy test as this would significantly delay the time to analgesia for patients in moderate to severe pain.

2 OBJECTIVES

Primary objectives:

- To assess the safety and tolerability of CT001 in pediatric participants with moderate to severe pain in an acute care setting
- To evaluate the analgesic effect of CT001 in pediatric participants with moderate to severe pain in an acute care setting

Secondary objectives:

- To assess medication errors in pediatric participants with moderate to severe pain in an acute care setting. (To be provided by site staff administering the IMP)
- To evaluate other analgesic effect of CT001 in pediatric participants with moderate to severe pain in an acute care setting.
- To evaluate the need of supplemental analgesics.
- To evaluate feasibility of CT001 in pediatric participants with moderate to severe pain in an acute care setting.

3 POPULATION

The study population will be recruited from children and young people aged 1 – <18 years (prior to their 18th birthday), who present to an ED following an isolated injury where immediate pain relief is judged to be needed.

3.1 Inclusion Criteria

To participate in the study, and prior to performing any study-related procedures, the following inclusion criteria must all be met:

1. Participant aged 1 to <18 years.
2. Attending an ED following an injury.
3. A pain intensity score corresponding to moderate or severe pain, as assessed by age relevant scales:
   - Age group ≥9 to <18 years: pain score 5 to 10 using the Numerical Rating Scale (NRS); self-reporting by the participant.
   - Age group ≥5 to <9 years: pain score 6 to 10 using the Wong-Baker FACES scale; self-reporting by the participant.
   - Age group ≥1 to <5 years: pain score 5 to 10 using the FLACC pain scale; assessed by site staff.
4. Evidence of signed and dated informed consent form, indicating that the participant and/or parent/ guardian (if participant younger than 16 years) has been informed of and has fully understood all pertinent aspects of the study as required for the age of the child in accordance with local legislation.

3.2 Exclusion Criteria

To participate in the study potential participants must not meet any of the following exclusion criteria:

1. Critical, life- or limb-threatening condition requiring immediate management.
2. Open fractures.
3. Participants with chronic pain.
4. Participants requiring oxygen therapy.
5. Clinically evident respiratory depression.
6. Clinically evident cardiovascular instability (e.g. pathological arrhythmia).
7. Known liver disease.
8. Known kidney disease.
9. Presence of other acute clinical or medical condition that may, in the opinion of the investigator, put the potential subject at risk when participating in the study, impact the participant's ability to participate in the study, or have impact on the study results, including being subject to head injury and / or altered consciousness.
10. A female of childbearing potential is eligible to participate if she verbally confirms not to be at risk of being pregnant or breastfeeding and agrees to follow the contraceptive guidance for 7 days after IMP administration.
11. Acute intoxication with drugs or alcohol, based on the judgement of the attending physician.
12. Participant showing abnormal nasal cavity/airway such as:
    a. major septal deviation
    b. evidence of previous nasal disease or surgery
    c. current significant nasal congestion due to common cold
13. History or presence of hypersensitivity or allergy to sufentanil or ketamine, a history of anaphylactic reactions, or a history of other allergy that, in the opinion of the investigator, contraindicates their participation.
14. Has received treatment with sufentanil and/or ketamine during the last 72 hours
15. Is currently participating in or has participated in an interventional clinical trial with an investigational compound or device in the 4 weeks prior to signing the informed consent/assent for this trial.
16. Previous enrolment in the present study.

3.3 Recruitment and Screening

Participants will be identified and recruited from the ED. The participant-targeted recruitment initiatives and any information given to potential participants and/or their parents or legal guardians will be submitted to, and approved by, the respective Ethics Committee(s) prior to implementation.

The Investigator is responsible for obtaining informed consent and assent (in accordance with local regulations), please see section 8.2. Information about the study may explained to the participant and parent/guardian by an experienced study nurse but the consent should be obtained by the investigator.

During the screening assessment, a participant ID number will be assigned for identification of the participants. The Investigator will maintain a participant ID Log for all participants who undergo

screening. If assessments required for screening have already been completed as part of standard treatment at the ED prior to participant/parent/guardian signing the ICF, historical data can be collected, see section 4.2.

After completion of screening (part 1), all participants deemed eligible to take part in this study will be enrolled. If a participant screen fails, this will be noted in a screen failure form.

3.3.1 Pregnancy and contraceptive guidance

Females that have reached menarche, will be excluded if they verbally state any possibility of being pregnant or if they are breastfeeding.

Eligible females that have reached menarche must use contraception for 7 days after IMP administration. Acceptable contraceptive methods include:

- Sexual abstinence
- Combined hormonal (estrogen and progesterone) contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner

3.4 Lifestyle considerations

3.4.1 Meals and dietary restrictions

Not applicable in an emergency setting. However, the time of last oral intake (fluids and solids) will be documented.

3.4.2 Activity restrictions

Ambulation is allowed between drug administration and any indicated medical procedures.

3.4.3 Driving and bicycling

Participants will be told not to engage in critical complex personal decisions, or operate heavy machinery, car driving or riding a bicycle on the day of the IMP administration.

4 STUDY PROCEDURES

4.1 Overall Study Design

This study is an open label multi-centre study evaluating the safety, tolerability, analgesic efficacy, and feasibility of IN CT001, on acute pain relief in pediatric participants in an acute care setting where acute pain relief is judged to be needed. The study comprises of 2 study parts on Day 1, and part 3 consisting of a follow up phone call (on Day 2-7). On Day 1, participants will be screened (Part 1), enrolled and treated (Part 2). For the overall study design, see Figure 1.

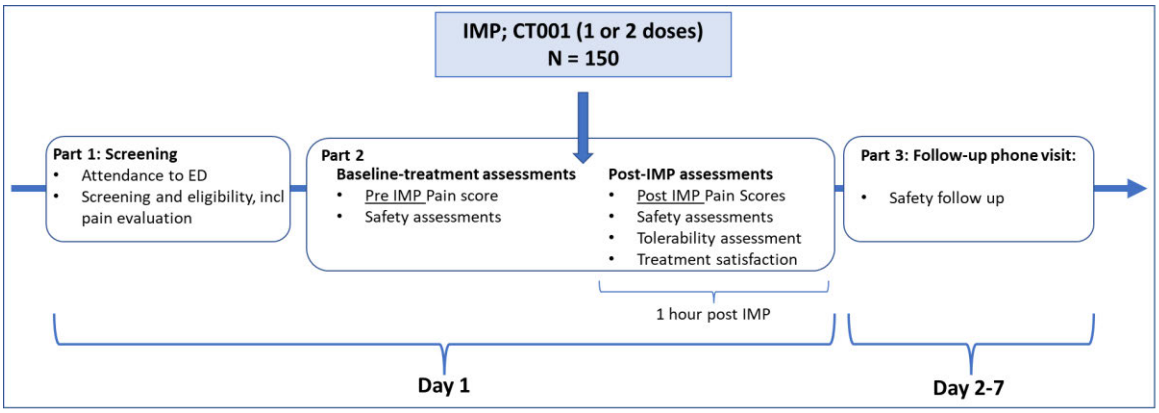

*Figure 1. **Schematic Study Design,***

ED; emergency department, IMP; investigational medicinal product.

Children and young people attending an ED who report moderate or severe pain will be eligible for enrolment in the study. In total, 150 evaluable participants will be included, with an estimated need to screen 180 subjects to reach the necessary number of evaluable patients. Each participant will receive one or potentially two consecutive doses of intranasally administered CT001 (with 10-15 min in-between).

All study related activities will take place in the acute care setting, including monitoring of vital signs (measurements of pulse rate, oxygen saturation and respiratory rate). The participating EDs will all contain appropriate equipment and drugs to address any complications from the trial medication, including standard airway/breathing life support equipment, rescue analgesia, and naloxone.

4.2 Clinic visits

Part 1; Screening (Day 1)

Potentially-eligible participants and their parents or legal guardian will be provided with written information about the study. Families who state an interest in participation will be asked to provide written informed consent +/- assent, as appropriate for the age group in accordance with local legislation. A patient ID number will then be assigned.

Following completion of the informed consent form (ICF), a formal screening assessment will be conducted, including assessment of eligibility according to the study inclusion and exclusion criteria. Pain scoring within the screening assessment will be conducted using the following pain intensity scores:

Age ≥9 years:	A 0-10 numerical rating scale (NRS) scale (10).
Age ≥5 to <9 years:	The Wong-Bake FACES scale (14).
Age ≥1 to <5 years:	The FLACC scale (15).

The same pain scale will be used for all subsequent study pain scores for that patient.

Any preceding data from the routine ED triage assessment (such as demographics, injury type, pain score, concomitant medications, and vital signs) can be utilized and transferred onto the screening electronic Case Report Form (eCRF).

The screening assessment will also include documentation of participant demographics, past medical history, and concomitant medications. If not already undertaken at the routine triage assessment, the participant will be weighed. Where a participant's injury makes weighing impractical, an estimated weight will be documented.

Females participants that have reached menarche, will be asked if it is any possibility tht thy could be pregnant. If they respond yes, they will not be eligible for the study. Females participants that have reached menarche and who are sexually active will be asked to follow contraceptive guidance for 7 days following IMP administration.

For further guidance on assessments at screening, see Study Assessment Chart Table 1.

Part 2; Baseline and IMP treatment (Day 1)

The baseline assessment will include a repeat pain score, sedation score, and measurement of the participant's vital signs (respiratory rate, pulse rate, oxygen saturation) if not already undertaken at

the routine triage assessment. Once the pre-treatment assessments are performed the IMP will be administered.

After administration of IMP, pain scores will be assessed at the following approximate intervals (10, 15, 20, 30, 45, 60 min post IMP), as specified in the Study Assessment Chart (Table 1). The actual timepoints for pain assessment relative to IMP administration will be recorded in the eCRF.

Unscheduled pain intensity scores will be measured and documented during any potentially painful intervention (e.g. during the application of a plaster cast for a fracture), prior to rescue medication or prior to premature study withdrawal.

Where pain relief at 10-15 min after the first IMP administration is insufficient (for example, a pain score >4/10 on NRS, or at the discretion of the treating investigator), a second IMP dose of similar strength and dose can be administered to the participant. In the case of insufficient pain relief after two doses of IMP, additional analgesic medication may be administered at the discretion of the treating investigator, in accordance with standard local practice. The medication, dose and time of administration will be recorded in the eCRF.

After administration of IMP, level of sedation, vital signs (pulse rate, peripheral oxygen saturation, respiratory rate), nasal tolerability and spontaneously reported adverse events will be assessed.

Pain scores and safety assessments should continue for 60 min after the last dose of IMP, or until additional analgesic treatment or procedures need to be initiated. For further guidance on assessments at the treatment and post-treatment visit (Part 2), see Study Assessment Chart, Table 1.

Feasibility and treatment satisfaction in relation to the IMP and route of administration will be assessed prior to ED discharge.

Treatment satisfaction will be addressed by using the following standardized question: "*How satisfied are you with the study drug that you/your child received? Please think about how it helped their pain, how it was given, any side effects, and how quickly you/your child recovered*". Respondents will answer using a 5-point Likert scale (very unsatisfied, unsatisfied, neutral, satisfied, very satisfied).

Acceptance of the intranasal route of administration will be assessed by the child. The healthcare professional will ask the child: "*If you were in this situation again and needed pain medication, would you like to receive the nasal spray (relative to getting an injection, tablet or suppositories for the pain)*? If not possible by the child, then by the parent/guardian.

Part 3; Text/telephonic follow-up for safety (Day 2-7)

On day 2-7 the parent/legal guardian (or patient if aged 16 to <18) will be contacted via text message (if possible), asking if the patient has experienced any side effects following discharge from the ED. If the reply is “yes” or the person does not respond to the text, the site investigator will attempt to contact them by phone to obtain further information about these adverse events. A total of 3 attempts will be made to make telephone contact. If all attempts are unsuccessful, the patient’s General Practitioner (GP) may be contacted for any relevant follow-up information. For further guidance on assessments, see Study Assessment Chart in Table 1.

*Table 1: **Study Assessment Chart***

Visit Number and Name	1 Screening	2 Baseline and IMP Treatment	3 Follow-up (phone)
Study day	**1**	**1**	**2-7**
Study Activities			
Signed Informed Consent	X		
Allocation of participant ID	X		
Inclusion/Exclusion Criteria	X		
Type of injury*	X		
Demographics*	X		
Relevant Medical and surgical history*	X		
Recent and Concomitant medication*[g)]	X	X	X
Weight*	X		
Peripheral oxygen saturation*		X	
Pulse rate*		X	
Respiratory rate*		X	
Sedation score [a)]		X	
Pain intensity assessment* [b)]	X	X	
Administration of IMP [c)]		X	
Adverse events/ Serious adverse events [d)]		X	X
Nasal tolerability [e)]		X	
Feasibility and Treatment satisfaction questions [f)]		X	

* if data from assessments performed prior to ICF signature are part of normal ED procedure they can be used in the study.

a) Sedation will be assessed immediately after pain intensity assessments using the UMMS score at baseline and at 10, 15, 20, 30, 45 and 60 min post-IMP. If a second dose of IMP is needed the sedation score will be performed at the same time points relative to the second dose.

b) Pain assessment will be performed using age-appropriate scales and they will be performed at screening, at baseline (before IMP administration), and at 10, 15, 20, 30, 45, 60 min post IMP. If a second dose of IMP is needed, the pain assessment timepoints will continue for 60 min after last IMP or until additional analgesics or procedures needs to be initiated. Unscheduled pain assessments should be done during any potentially painful intervention (e.g. during the application of a plaster cast for a fracture), prior to rescue medication or prior to premature study withdrawal.

c) IMP will be administered to the participant while sitting in an upright position using the appropriate strength depending on the participant's weight. See more info in the IMP section and in the IMP manual.

d) Adverse events will be collected spontaneously at all visits using open questioning.

e) Nasal tolerability and irritation will be assessed using combined participant reported symptoms and investigator examination/inspection of the nasal cavities. Nasal tolerability will be performed twice; appr 30 min and 60 min after the *last* IMP administration (following pain, sedation and vital signs assessments).

f) Treatment satisfaction will be addressed by asking the standardized questions "*How satisfied are you with the study drug that you/your child received? Please think about how it helped their pain, how it was given, any side effects, and how quickly you/your child recovered*". Respondents will answer using a 5-point Likert scale (very unsatisfied, unsatisfied, neutral, satisfied, very satisfied). Feasibility (i.e. acceptance of nasal administration) will be addressed by the healthcare staff asking the child: *If you were in this situation again*

and needed pain medication, would you like to receive the nasal spray? If not possible by the child, the parent/legal guardian will assess nasal acceptability.

g) Any medication given for AEs during the time from enrolment to follow up should be entered in the eCRF. Any 'rescue medication' (described as additional analgesics due to insufficient effect of IMP during the 60 min after the last dose of IMP), should be entered in the eCRF. The time given should also be noted.

4.3 Assessments

Assessment results will be recorded in the eCRF, as applicable.

4.3.1 Medical and surgical history

A verbal medical and surgical history will be collected from the participant/legal guardian as part of admission procedures and recorded as historical data in the source notes and eCRF. Medical history will not be verified by referring to existing participant notes or by contacting the participant's General Practitioner, for example. Due to the acute nature of this protocol in an ED setting, the scope of the exclusion criteria, the short duration of the participant within the study and the short acting nature of the IMP, verification of medical history is not reasonably practical.

4.3.2 Pain intensity assessments

The pain resulting from injury causing the emergency visit will be quantified. The participant will be introduced to the age-appropriate pain scale and overall pain will be assessed, with no distinction made between spontaneous pain and any procedural pain.

Immediately prior to administration of the IMP (baseline), the pain intensity will be rated using the applicable tool (see below). Subsequent pain assessments will be performed at 10, 15, 20, 30, 45, and 60 min post IMP administration. If a second dose of IMP is administered after 10-15 min, the pain assessment schedule will be reset, and pain will be measured at 10, 15, 20, 30, 45, and 60 min after the second dose of IMP, or until additional analgesics or procedures needs to be initiated.

Unscheduled pain intensity scores will be measured and recorded during any potentially painful intervention (e.g. during the application of a plaster cast for a fracture), prior to rescue medication or prior to premature study withdrawal.

Age-appropriate pain intensity assessment tools will be used:

Age ≥9 years: The Numerical Rating Scale (NRS) will be used. The NRS scales consists of a Likert scale, anchored with numbers 0-10, with 0 marked "No pain" and the right end (10) marked "Worst pain imaginable". The patient will state the number representing their current level of pain, and the study staff will circle the applicable number on the CRF page (see Appendix A).

Age ≥5 to <9 years: The visual analogue scale modified with six faces developed by Wong-Baker (Wong-Baker FACES pain rating scale) will be used. Numerical values (0, 2, 4, 6, 8, 10) are listed for each face (Wong et al, 2001, see Appendix B).

Age 1 to <5 years: The study investigator will provide an assessment of pain, using the FLACC scale (Merkel et al, 1997, see Appendix C).

4.3.3 Assessment of sedation

The level of sedation will be assessed using the University of Michigan Sedation Score (UMSS, Appendix D). The UMSS has been validated for the assessment of procedural sedation in children. Level of sedation will be assessed at baseline (i.e. pre-IMP administration) and at 10, 15, 20, 30, 45, and 60 min post IMP immediately following each pain assessment. If a second dose of IMP is needed the sedation score will be performed at the same time points relative to the second dose.

4.3.4 Vital signs

The following vital signs will be measured at baseline and post IMP administration and recorded in the eCRF:

- Pulse rate (bpm): will be recorded from the pulse oximeter.
- Blood oxygen saturation (%), assessed by pulse oximetry (non-invasive method).
- Respiratory rate (breaths per minute).

The vital signs will be measured immediately after the pain and sedation assessments, at the same times points, i.e. at 10, 15, 20, 30, 45, and 60 min post IMP, or until additional analgesics or procedures needs to be initiated. If values are not within normal range after 1-hour, vital sign measurements can be continued until ED discharge or until additional procedures need to be initiated.

4.3.5 Assessment of the nasal tolerability

Nasal tolerability/irritation will be assessed for all patients based on combined participant reported symptoms and investigator examination/inspection of the nasal cavities. The symptoms and signs can include sneezing, redness, itching, nasal discharge, local tenderness, swelling or other nasal irritation. Nasal tolerability/irritation will be assessed at 30- and 60-min post IMP administration (following pain, sedation and vital sign assessments). The 30 and 60 minute nasal tolerability timepoints should be taken from the *last* dose of IMP i.e. if a second dose of IMP is required, nasal tolerability should then be performed 30 and 60 minutes from the second dose. Any unpleasant symptoms from the nose during or after administration of the IMP reported by the participant will be recorded as adverse events.

4.3.6 Assessment of medication errors

Medication errors will be assessed by feedback from site staff that administer the IMP. If they eg do not switch between nostrils when dosing CT001, or give a different number of sprays than required per IMP manual.

4.3.7 Need for additional analgesics

In the case of insufficient pain relief after two doses of IMP, additional analgesic medication may be administered at the discretion of the treating investigator, in accordance with standard local practice. The type of rescue medication, dose and time of administration will be recorded in the eCRF. If a participant is given additional analgesics during the study, the pain assessments after administration of rescue medication will not be included in the efficacy analyses. This will be further described in the statistical analysis plan.

4.3.8 Demographics and weight

The bodyweight (in kg) of the participant will be measured during screening. Where a patient's injury makes weighing impractical, an estimated weight will be documented. Recording of demographics (sex, date of birth, ethnicity) will also be performed during screening.

4.3.9 Adverse events

See section 6.3 Adverse Events and Serious Adverse Events.

4.3.10 Concomitant medication

The following medications will be reported:

- Prescription medications within the previous 7 days.
- Over-the-counter medications within the previous 24 hours.
- IN medications within the previous 48 hours.

4.3.11 Any medication given for AEs during the time from enrolment to follow up should be entered in the eCRF. Any 'rescue medication' (described as additional analgesics due to insufficient effect of IMP during the 60 min after the last dose of IMP), should be entered in the eCRF. The time given should also be noted.Feasibility / Treatment satisfaction

Feasibility / treatment satisfaction in relation to the IMP and route of administration will be assessed prior to ED discharge.

Treatment satisfaction will be addressed using the following standardized question: "*How satisfied are you with the study drug that you/your child received? Please think about how it helped their*

pain, how it was given, any side effects, and how quickly you/your child recovered". Respondents will answer using a 5-point Likert scale (very unsatisfied, unsatisfied, neutral, satisfied, very satisfied).

Feasibility (i.e. acceptance of nasal administration) will be addressed by the healthcare staff asking the child: *If you were in this situation again and needed pain medication, would you like to receive the nasal spray (relative to an injection, tablet or suppository for the pain)?* If not possible by the child, the parent/legal guardian will assess nasal acceptability. Answers will be "yes", "no", "I don't know". If not possible by the child, then the parent/guardian.

4.3.12 **Text/telephonic follow-up for safety**

On day 2-7 the parent/legal guardian (or patient if aged 16 to <18 if in accordance with local legislation) will be contacted via text message, asking if the patient has experienced any side effects following discharge from the ED. If the reply is "yes" or the person does not respond to the text, the site investigator will attempt to contact them by phone to obtain further information about these adverse events. A total of 3 attempts will be made to make telephone contact. If all attempts are unsuccessful, the patient's General Practitioner (GP) may be contacted for any relevant follow-up information. The patient/ legal guardian(s) may, at any time during the study, contact the Principal Investigator, to discuss any drug experiences if needed. If it is not possible to reach the parent/legal guardian or the GP for the follow up phone call (on Day 2-7), then it should be stated that the patient is lost to follow up.

4.4 **Participant Withdrawal**

The Investigator will explain to the participant and legal guardian that they have the right to withdraw from the study at any time, and that this will not prejudice any future treatment. A participant who has consented to the study but not yet received IMP will be considered a screen failure if they decide to withdraw consent prior to receiving IMP. Once a participant has been administered IMP and subsequently decides to withdraw consent, the participant would be considered withdrawn. The reason for any kind of withdrawal must be recorded in the eCRF.

Reasons for withdrawing from may be:

- Unacceptable adverse events
- Participant or guardian's request
- Investigator's discretion
- Intercurrent illness

Whenever a participant is withdrawn from the study, the reason(s) of why the participant was withdrawn from the study should be recorded. All documentation concerning the participant must be as complete as possible, however, no new information can be collected if the participant or legal guardian has withdrawn his/her consent/assent to further study participation.

4.5 Replacement of participants

In total, 150 evaluable participants will be included and exposed to IMP. If a participant/legal guardian withdraws his/ her consent prior to IMP dosing, he/ she will be replaced. If a participant is withdrawn due to technical reasons or due to a surgical unrelated medical complication, he/ she will be replaced.

Rescreening of participants will not be allowed.

5 INVESTIGATIONAL MEDICINAL PRODUCT

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

5.1.1 [redacted]

[redacted]

The handling and storage will be further detailed in the IMP manual.
The IMP will be stored at room temperature (2-25 °C) at the study site in a secure area (a locked cabinet or drug storage room), protected from unintended use. A temperature log will be kept.
IMPs will be labelled according to local requirements.

5.1.2 Non-investigational medicinal products (NIMPs)

Rescue medication

Rescue medication can be given on the discretion of the investigator at any time in case of insufficient pain relief of IMP. Rescue medication should be given in accordance with local clinical practice. The type of rescue medication, dose and time of administration will be recorded in the eCRF.

5.2 Supply, Packaging, Labelling, Handling and Storage

The IMP will be manufactured, packaged, study labelled, batch certified by a qualified person (QP), and distributed in accordance with the principles of *Good Manufacturing Practice* and *Good Distribution Practice*, under the responsibility of Cessatech (or its designee).
IMP is prepared for dosing according to instructions. Detailed instructions for the preparation and handling of IMP will be provided by sponsor.
The wording on the participant-specific labels will be in accordance with *Good Manufacturing Practice* regarding labelling and national and/or local regulatory requirements.

5.3 Dosage and Administration

Dosing of CT001 in children is presented in mcg/kg (SUF) and mg/kg (KET). [redacted] to allow for simple dosing instructions while keeping an adequately narrow dose range around the target dose. This approach and the below dosing chart (Table 2) have been endorsed by the EMA.
The below dosing table described one dose administration, which then can be repeated once after 10-15 min, in the case of insufficient pain relief. Actuations should be given in alternating nostrils.

[redacted]

The dose administration is also be described in a separate IMP manual.

5.4 Number of Participants Treated in Different Age Groups

Participants from 1 to <18 years of age (inclusive) will be enrolled into the study. The aim will be to enrol the following minimum number of participants in each age group:

Age 1 - <5 years: 20 participants
Age 5 - <9 years: 40 participants
Age 9 - <18 years (inclusive): 40 participants

The remaining 50 participants can be flexibly enrolled into the age groups. Deviations to the above numbers may be accepted in case of recruitment challenges in some age groups.

5.5 IMP Accountability

All IMP for this study must be always retained in a safe place. Only personnel authorised by the PI at the site should dispense and administer the IMP. The investigator or pharmacist must complete an IMP accountability log, documenting product dispensed and used. This will be verified by the study monitor prior to destruction. Remaining IMP will be sent for destruction at the local hospital pharmacy, and this will be documented with a destruction certificate. If local pharmacy cannot destroy IMP, it can be returned for destruction according to the IMP manual.

6 RESPONSE VARIABLES AND ENDPOINTS

6.1 Assessment of Efficacy

6.1.1 Primary efficacy variable

To investigate the analgesic efficacy of IN CT001 in pediatric participants in the acute care setting experiencing pain of moderate to severe intensity.

- Analgesic efficacy will be assessed as changes in pain intensity from baseline using age relevant scoring instruments (FLACC score for ages ≥ 1 year to < 5 years, the Wong-Baker faces scale from ages ≥ 5 years to < 9 years, and the 0-10 Numerical Rating Scale (NRS) from ages 9 and above). The pain assessments will be made prior to the first IMP dose (baseline) and then at the following timepoints: at 10, 15, 20, 30, 45, 60 min post first IMP dose. The primary efficacy endpoints will be the responder rate i.e., the percentage of participants that has a pain intensity score at 4 or below at 15 min and at any timepoint during 30 min post IMP.

6.1.2 Secondary efficacy variable

To evaluate additional analgesic effect of CT001 in pediatric participants with moderate to severe pain in an acute care setting

- Maximum change from baseline in pain intensity within 30 min post IMP administration.
- Number and proportion of participants that achieve a 30% reduction in pain intensity relative to baseline within 30 min post IMP.
- Change from baseline in pain intensity at 10, 15, 20, 30, 45 and 60 min post IMP.
- Derived variables such as area under curve (AUC), peak change in pain intensity from baseline, and duration of effect will be calculated from the recorded pain assessments.

To evaluate the need for supplemental analgesic medication during the study period

- Number and proportion of children receiving additional analgesics, as assessed by timepoint.

6.2 Assessment of safety and tolerability

6.2.1 Primary safety and tolerability variables

To investigate the safety and tolerability of IN CT001 in pediatric participants in the acute care setting experiencing pain of moderate or severe intensity.

- Sedation as assessed by sedation score on the University of Michigan Sedation Scale (UMSS) (Malviya et al, Anesthesiology 2004) at the following timepoints: baseline and 10, 15, 20, 30, 45 and 60 min after first IMP administration. If a second IMP dose is needed, sedation will be performed at the timepoints relative to first IMP administration.
- Respiratory depression, assessed by respiratory rate.
- Peripheral Oxygen saturation, as assessed by peripheral oximetry.
- Cardiovascular stability, as assessed by pulse rate.
- Number of reported Adverse Events, graded by intensity and severity.
- Number of AEs reported per participant.
- Local nasal irritation as assessed by combined participant and investigator feedback at 30 and 60 min post IMP administration.

6.2.2 Secondary safety and tolerability variables

To evaluate the feasibility/treatment satisfaction of the nasally administered CT001 for acute pain relief in pediatric participants in the emergency setting.

- Treatment satisfaction as assessed by responses to the question: "*How satisfied are you with the study drug that you/your child received? Please think about how it helped their pain, how it was given, any side effects, and how quickly you/your child recovered*". Respondents will answer using a 5-point Likert scale (very unsatisfied, unsatisfied, neutral, satisfied, very satisfied).
- Feasibility (i.e. acceptance of nasal administration) will be addressed by the healthcare staff asking the child: *If you were in this situation again and needed pain medication, would you like to receive the nasal spray (relative to an injection, tablet or suppository for the pain)?* If not possible by the child, the parent/legal guardian will assess nasal acceptability. Answers will be "yes", "no", "I don't know".
- Medication errors, defined as any deviation in the IMP administration instructions that result in higher or lower dose than planned. Examples may include erroneous priming of the pump, too few/many pumps administered, etc.

6.3 Adverse Events and Serious Adverse Events

The Investigator should ensure thorough collection of all adverse events (AEs) and concomitant medication information associated with each participant. The Investigator should ask the participant to report any feeling of being unwell or different from usual in any way during the clinic visit to ensure that adverse event (AE) information is recorded in the participant's source notes and is then subsequently entered into the eCRF. Adverse events can be events or symptoms reported by the participant. They can also be symptoms and signs observed by study staff.

All relevant responses from the participant will be recorded in the source notes and eCRF on an AE form and graded on severity (mild, moderate, severe), seriousness and relationship to IMP (unlikely, possibly, probably). Whenever possible a diagnosis should be given and not just a list of signs and symptoms. For further details regarding the classification of AE, please see below.
All AEs are to be reviewed by the Investigator while ongoing, and subsequently documented at the point of resolution. All AEs classified as serious are to be immediately brought to the attention of the Investigator by site staff for review and action. All ongoing AEs will be followed up by the Investigator until participant discharge or resolution (i.e. AE's can thus be followed longer than 60 min post IMP is deemed needed). Additional clinic visits may be scheduled by the Investigator to follow-up on AEs according to their clinical judgement.

6.3.1 Baseline symptoms

A baseline symptom is defined as an event that occurs between signing of the assent / ICF until the first administration of IMP (i.e. an event that occurs during the screening period). Such events are not classified as AEs and will be recorded as baseline symptoms in the Medical History Log in the eCRF.

6.3.2 Definitions of Adverse Events

Adverse Event (AE):

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including clinically significant abnormal values from relevant tests, such as clinical safety laboratory tests, ECGs, vital signs), symptom, or disease temporally associated with the use of an IMP, regardless of whether it is considered related to the IMP.
A baseline symptom is any medical event in a clinical study subject that occurs after he/she signed the ICF up until the first administration of IMP.
A treatment emergent AE (TEAE) is any AE not present, prior to the initiation of IMP administration or any event already present that worsens in either intensity or frequency following exposure to the IMP.
Only TEAEs are collected in this study (i.e., events occurring between screening and the first IMP administration are regarded as baseline symptoms and should not be recorded in the AE log in the eCRF.

Serious Adverse Events (SAEs):

An SAE is any AE that:

- results in death

- is life-threatening (this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent any of the SAEs defined above)

Examples of medically important events are intensive treatment in an emergency room for allergic bronchospasm or blood dyscrasias, convulsions that do not result in hospitalization, development of drug dependency, and drug abuse.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Non-serious adverse event:
Is any adverse event that does not meet the definition of an SAE.
If there is any doubt as to whether an adverse event meets the definition of an SAE, a conservative viewpoint must be taken, and the adverse event must be reported as an SAE.

Adverse Reaction:
All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. For marketed medicinal products, an adverse reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

Unexpected Adverse Reaction:
An adverse reaction, the nature or severity of which is not consistent with the applicable product information for the test product (Investigator's Brochure).

Suspected Unexpected Serious Adverse Reaction (SUSAR):
Any serious adverse reaction that might be related to the study medication and are unexpected according to the definition above.

Overdose:

Is a dose administered to a participant that exceeds the dose prescribed to that participant. Any overdose (and associated symptoms) must, at a minimum, be recorded as a non-serious adverse event.

6.3.2.1 Severity

Note that severity is a description of the intensity of the AE and is not to be confused with seriousness for which the definitions in 6.3.2 apply. Both seriousness and severity of an AE need to be assessed independently.

Mild:

The adverse event is transient and easily tolerated.

Moderate:

The adverse event causes the subject discomfort and interrupts the subject's usual activities.

Severe:

The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

6.3.2.2 Relationship to IMP

The causal relationship between the IMP and the AE should be indicated, using a modified WHO-UMC causality categories, see Table 3.

Table 3. ***WHO-UMC Causality Categories***

Causality term	Assessment criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs

	• Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations

For data analysis and SAE reporting purposes, AEs classified as 'unlikely' will be regarded as 'not related'; AEs classified as 'possible', 'probable/likely' and 'certain' will be regarded as 'related'.

6.3.3 Follow-up of unresolved AEs

Participants experiencing adverse events will be monitored with appropriate clinical evaluation and laboratory tests as indicated by the principal investigator. All subjects with adverse events will be followed until satisfactory recovery or stabilization are attained.

6.3.4 Reporting of adverse events

All Adverse Events must be recorded in the case report form, defining relationship to IMP and severity.

As soon as the Investigator is aware of a potential Serious Adverse Event (SAE), he/she should contact the local SMERUD monitor by phone, fax or e-mail, and in any case no later than 24 hours after the knowledge of such a case.

If identification of the event occurs outside of office hours, the emergency phone number described in the Investigator Site File may be used. At the time of the call, the Investigator must provide as a minimum requirement the participant enrolment number, birth date, nature of the SAE, and a preliminary assessment of causality. The Investigator should follow up the initial notification of the potential SAE by faxing a copy of the SAE reporting form to SMERUD at the number provided in the Investigator Site File. The faxed SAE reporting form should be received at SMERUD within 24 hours after knowledge of such a case.

Smerud Medical Research International AS
E-mail: pharmacovigilance@smerud.com
Fax: +47 23 27 20 01
Tel: +47 23 27 20 00

Follow-up information on an existing SAE that is fatal or life-threatening should be reported by the Investigator to SMERUD within 5 days after the initial report. Where appropriate, hospitalization or autopsy reports should be made available. All Serious Adverse Events will be followed up until resolution (i.e., asymptomatic, stabilization or death).

6.3.5 **Reporting of suspected unexpected serious adverse reactions**

Suspected unexpected serious adverse reactions (SUSARs) will be reported by SMERUD according to appropriate Competent Authority and Ethics Committee requirements. SMERUD will report SUSARs to Investigators on a regular basis according to ICH Good Clinical Practice and to local regulations. SUSAR reporting to the Competent Authorities and Ethics Committees will be performed according to local regulations in an unblinded manner. The Competent Authorities will be notified of all SUSARs through the Eudravigilance database.

Fatal and life-threatening SUSARs should be reported by SMERUD as soon as possible to the Competent Authorities and Ethics Committees according to local regulations, and in any case no later than seven calendar days, after knowledge by SMERUD of such a case. Relevant follow-up information on the case will be subsequently communicated within an additional eight days. All other SUSARs shall be reported to the Competent Authorities concerned and to the Ethics Committee concerned, according to local regulations, as soon as possible but within a maximum of fifteen days of first knowledge by SMERUD.

7 STATISTICAL METHODOLOGY AND DATA MANAGEMENT

The principal features of the statistical analyses to be performed are described in this section. A more technical and detailed elaboration of the principal features will be presented in a separate Statistical Analysis Plan (SAP), which will be signed and approved prior to database lock (DBL).

7.1 Estimation of Sample Size

So far, data from 375 children on IN sufentanil/ketamine show a safe and tolerable combination (data from PDC 01-0201, PDC 01-0203 and PDC 01-0206). Thus, from a safety perspective it is expected that 150 patients will be sufficient to capture and confirm the adverse event profile of the IMP. Furthermore, a sample size calculation was made for the primary efficacy endpoint on the basis of expecting a responder rate of 60%. A previous study reported a responder rate of 71.6 %, defined as pain intensity <= 3 at 30 min post IMP (16). With a sample of 113 patients, a one-sample one-sided proportion design would provide at least 80% power to show that the responder rate is more than to 60%, with a significance level of 5%. Accounting for an approximate 25% dropout rate the resulting sample size is 150.

7.2 Study Population

The analysis of data will be based on different subsets according to the purpose of analysis, i.e., for efficacy, safety/tolerability, respectively.
The decision regarding validity of data for each of the analysis sets will be made before DBL.

Enrolled population

The enrolled population consists of all enrolled participants regardless of receiving study treatment.

Full Analysis Set (FAS)

The full analysis set (FAS) will consist of all participants who received at least one dose of study treatment. The FAS follows the intention-to-treat (ITT) principle, i.e. participants will be analysed, regardless of whether treatment was received as planned. The FAS will be used for the analysis of primary and secondary objectives.

7.3 Method of imputation

The amount of missing data will be reported as appropriate, and no other imputation will be performed.

7.4 Method of statistical analyses

All data will be presented as descriptive analyses only. Continuous variables will be summarised using descriptive statistics (number of participants, mean, standard deviation [SD], minimum, median, maximum) by age group and as total. Categorical variables will be summarised in frequency tables (frequency and proportion) by age group and as total. Graphical presentations will be used as appropriate. All changes from baseline endpoints are calculated as the value of the corresponding timepoint minus the value at baseline.
Variables that are based on ordinal scales, such as pain intensity, will be summarized using median and interquartile range.

7.4.1 Analyses addressing the primary objectives

Primary safety and tolerability analysis
For assessment of safety and tolerability, a multidimensional analysis using descriptive statistical methods will be conducted as follows:

Adverse Events
The number of subjects with adverse events, with possible treatment related adverse events, and with serious adverse events (SAE) will be summarised using counts and percentages of subjects by age groups. The number and percentage of subjects with adverse events by body system and preferred term will be summarised by age group. Adverse event severity and relationship to treatment will be summarised by body system, preferred term, and age group. Separate tables may be produced for SAEs depending on the number of SAEs occurring in the study. A 95% confidence interval will be computed for each percentage/proportion of adverse events.

Respiratory Depression, Peripheral Oxygen Saturation, and Cardiovascular Stability
These will be assessed by vital signs parameters of respiratory rate, peripheral oximetry, and pulse rate respectively. Measured values and changes from baseline will be summarised by mean, standard deviation (SD), 95% CI, median, minimum and maximum for each timepoint by age group and for all participants. Graphical representation of the measured values and changes from baseline in the form of boxplots will be produced for each timepoint (horizontal axis) by each age group and for all participants.

Nasal irritation/Tolerability
– The number of participants with nasal irritation will be summarised using counts and percentages of participant for each timepoint (30 and 60min post IMP administration) by age groups, dose level, and type of nasal irritation. A 95% CI of the percentage will be computed and reported.

Sedation

the UMSS scores at assessment timepoints (baseline and 10, 15, 20, 30, 45, and 60 min after IMP administration) will be summarised using the median and IQR by age group and dose level. Graphical representations of UMSS scores in the form of boxplots will be produced for each assessment timepoint (horizontal axis) and for each age group. A 95% confidence interval of the mean UMSS score for each time point and by age group if appropriate (i.e., if data is normally distributed.

Primary efficacy analysis

The primary efficacy endpoint will be reported using descriptive statistics only. The analgesic effect will be assessed as the proportion of participants that has a reduction of pain intensity to a score of 4 or below at 15 min and within 30 minutes post IMP (relative to baseline). A 95% confidence interval for the proportion of the participants with a pain reduction of 4 or less within the first 30mins post IMP will be evaluated and reported for each age group and for all subjects.

The pain intensity score is measured using different scales for each of the three age groups:

- Numerical Rating Scale, a self-reported ordinal, categorical scale with values 0-10, interval 1 for subjects aged 9 and less than 18.
- Wong-Baker, a self-reported ordinal, categorical scale with values 0-10, interval 2 for subjects aged 5 and less than 9.
- FLACC, an ordinal, categorical scale with values 0-10, interval 1 for subjects aged 1 and less than 5. Pain intensity assessment for this age group to be conducted by the investigator.

Given that the pain intensity is measured using different scales for each of the three age groups, subgroup analyses stratified by measurement scale may be appropriate. Graphical representation of pain intensity scores measured within 30mins post IMP administration will be produced in the form of boxplots for each age category/assessment scale.

7.4.2 Analyses addressing the secondary objectives

Secondary safety and tolerability analysis

Treatment Satisfaction

The general treatment satisfaction score is an ordinal, categorical variable which will be reported as median and IQR by age group and for all subjects.

Feasibility (Acceptance of Nasal administration)

The categorical responses 'Yes', 'No' and 'I don't know' by the child or their caregiver to the question: '*If you were in this situation again and needed pain medication, would you like to receive the nasal spray (relative to an injection, tablet or suppository for the pain)?'* will be summarised counts and percentages by age group and for all subjects. Frequency graphs may also be used to summarise the data.

Medication Errors

Counts and percentages by age group and dose level will be used to summarise deviations in the administration of the IMP that result in higher or lower dosage than planned.

Secondary efficacy analysis

Need for Supplemental Medication

The number of children receiving additional analgesics will be summarized using counts, frequency tables and graphs by type, dose, and timepoint.

Maximum change in pain intensity within 30 min post IMP administration

Maximum change in pain intensity within 30 min post IMP administration (relative to baseline) will be computed for each subject. The maximum change will be summarised by the median and IQR by age group and dose level. Average time from IMP to maximum change in pain intensity will also be reported.

30% (or more) reduction in pain intensity within 30 min post IMP administartion

The number of subjects that achieve at least 30% reduction in pain intensity relative to baseline within 30 min post IMP administration will be summarized using counts and percentages (frequency tables) and reported by type, dose level, and timepoint.

Change in pain intensity

The change in pain intensity from baseline will be computed for each subject at 10, 15, 20, 30, 45 and 60 min post IMP and this parameter will be summarized by the median and IQR and reported by age group and dose level.

7.5 Data Collection / Case Report Forms

Data will be collected using an electronic data capture (EDC) solution. Electronic Case report forms (eCRFs) will be utilised for recording data from each subject meeting the eligibility criteria and being

included in the study. The eCRF system, Viedoc™, will be available on an internet portal accessible through any standard computer device with internet access. All study staff responsible for entering data into the eCRF system will be trained at the Investigator meeting and/or by the Clinical Research Associate (CRA) prior to the start-up of the study. A personal log-in will be provided for all responsible personnel to allow for an audit trail relating to the study data to be maintained. No clinical trial information will be transferred via the eCRF system until the site has been qualified through completion of a validation eCRF.

All evaluations performed shall be entered in a timely manner into the eCRF by a member of the site staff delegated responsibility for this specific task by the Principal Investigator (PI) of the clinical site. It is the responsibility of the Investigator to ensure that the eCRFs are properly completed. The data in the eCRFs should be consistent with the relevant source documents. The Investigator will sign the designated signature fields of the eCRF data entry screens to confirm that the information on each screen is accurate and complete. All data must be stored in an unidentifiable form treated with strict confidentiality in accordance with applicable data protection regulations.

Captured data will be monitored electronically and Source Data Verification (SDV) will take place at the site, i.e. relevant information (as outlined in the monitoring plan) will be verified against the individual subject records unless the eCRF is considered source data.

Any inconsistencies will be presented as queries; either as automatically generated queries if raised by the logical data checks of the eCRF system, or by manually generated queries if raised by the data validation checks or the SDV performed by the Data Manager (DM) or the CRA respectively. Queries shall be resolved in a timely member by a trained member of the site staff.

7.6 Data Management

Data will be transmitted electronically into the web-based EDC system. Upon receipt, data will be coded according to pre-specified dictionaries and in accordance with the CROs Standard Operating Procedures (SOP). The handling of data, including data quality control, will comply with all applicable regulatory guidelines.

8 REGULATORY AND ADMINISTRATIVE PROCEDURES

8.1 Institutional Review

The procedures set out in this study protocol are designed to ensure that the Sponsor, the CRO and Investigator abide by the principles of the Guideline for Good Clinical Practice (GCP) of the International Conference of Harmonization (ICH) Good Clinical Practice as last amended in 2016, in the conduct, evaluation and documentation of this study (17). Further, the study will be conducted

in accordance with the moral, ethical and scientific principles governing clinical research as set out in the World Medical Association. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. World Medical Association 1964, Amended 2013. The study will further be carried out in accordance with any additional local legal requirements.

The Protocol and the Subject Information Sheet / Informed Consent Form / Assent Form will be approved by the relevant Competent Authorities and Ethics Committees, and possibly other public bodies according to local requirements before commencement. If a protocol amendment is necessary, this will be prepared with the agreement of the Principal Investigator and signed by the relevant parties. If the amendment is considered substantial, it will be submitted to the Competent Authorities and Ethics Committees, and possibly other public bodies according to local requirements for review and approval. The protocol amendment will not be implemented before the required approvals are obtained. Minor amendments which do not affect the safety or physical or mental integrity of the clinical trial subjects or the scientific value of the trial (i.e. non-substantial amendments) will not be submitted to Competent Authorities or Ethics Committees.

SUSAR reports and Periodic Safety Reports will be sent to Competent Authorities and Ethics Committees according to local regulations.

8.2 **Subject Information / Informed Consent**

In the following, the word study subject includes the participant and/or the accompanying parent/legal guardian.
The Investigator is responsible for giving the study subject full and adequate verbal and written information about the nature, purpose, possible risk, and benefit of the study. Information about the study and obtaining consent may be delegated to an experienced study nurse. Study subjects must also be notified that they are free to withdraw from the study at any time. The subjects should have reasonable time to read and understand the information before signing. The Investigator is responsible for obtaining signed informed consent from all subjects before including the subject in any study related procedures. A copy of the participant information and of the signed Informed Consent Form / Assent Form in local language, will be given to the subjects. One original copy of the signed Informed Consent form / Assent Form will be kept by the subject and one copy will be retained at the study site.

8.3 Subject Confidentiality and Data Protection

8.3.1 Subject confidentiality

The Investigator must ensure that subject's confidentiality will be maintained. eCRFs or other documents submitted to the sponsor should only identify subjects by their initials and study number. The Investigator should keep a separate log of subject codes and names. Documents not for submission to the Sponsor, e.g., subject's completed Consent Forms, should be retained by the Investigator in strict confidence.

The Investigator is required to record primary efficacy and safety data, concomitant medication, and subject progress in the subject's file/notes/medical record.

The subject's medical records (source data) will be reviewed by the study monitor and possibly by other sponsor personnel or regulatory authorities, to verify adequate source documentation, accuracy, and completeness of eCRFs. The review will be conducted with strict adherence to professional standards of confidentiality. No participant identifiable data will be taken out of the investigator site.

All subjects screened for the study will have their initials and birth date entered chronologically on the Subject Screening Log at the initial visit. An explanation for exclusion from admission to the protocol is to be provided on the Subject Screening Log.

8.3.2 Data Protection

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the potential effects of the study drug. Collection, handling, and storage of personal data from the clinical trial will only take place as described in the PIS/ICF as well as in section 7.5 (Data Collection) and in accordance with the General Data Protection Regulation (EU 2016/679), current EU Clinical Trial Regulations (regulation 536/2014) and any applicable local regulations.

A dedicated Data Protection Officer (DPO) employed by SMERUD is registered at the Data Protection Authority. The DPO will always supervise that the subjects' data protection is maintained by auditing and approving the electronic data capture (EDC) provider, ensuring data protection procedures are in place and ensuring that the annual audit programs include also checks of subject data protection.

8.4 Subject Treatment Plan

The subjects are otherwise generally healthy children attending the ED for different indications.

8.5 GCP

The procedures set out in this study protocol are designed to ensure that the Sponsor, the CRO and Investigator abide by the principles of the Guideline for Good Clinical Practice (GCP) of the International Conference of Harmonization (ICH) Good Clinical Practice as last amended in 2016, in the conduct, evaluation and documentation of this study.

8.6 Essential Documents

The ICH guideline for GCP lists several essential GCP documents required prior to, during and after the conduct of the study. It is the responsibility of the monitor to ensure that the Investigator is always provided with a copy of such documents prepared by the study management, and it is likewise the responsibility of the Investigator to provide the monitor with essential documents prepared by the Investigator or the local Ethics Committee.

Record Retention

The investigator site file, eCRFs and all medical records upon which the eCRFs are based (source data) must be kept for at least 25 years or according to local legislation whichever is the longest after completion of the study. Image carriers or other data carriers may be used for this purpose. The documentation should be easily retrievable and readable during the entire archiving duration.

8.7 Monitoring / Quality Control

Prior to the start of the study, the Study monitor will review the protocol and eCRFs with the Investigator and his/her staff. The Investigator will be visited on a regular basis by the study monitor, who will check study procedures, including safety assessments, IMP handling, data recording and perform source data verification (SDV). The study monitor must be allowed to review subject records to confirm that required protocol procedures are being followed and check consistency between subject record and eCRF data. Incorrect or missing entries in the ECRFs will be queried and must be corrected in a timely manner.

8.8 Quality Assurance

During or after the study is completed, sponsor representatives or regulatory authorities may wish to carry out an audit or an inspection. These representatives must have the same access to study data and subject source data as the study monitor.

8.9 Insurance and Liability

Participants taking part in this clinical study are insured by the Sponsor against any injury caused by the clinical study, in accordance with the local regulatory requirements. A copy of the insurance certificate will be provided to each investigator and will be filed in the investigator's file at the sites

and in the clinical trial's Trial Master File (TMF). The investigator must notify the Sponsor immediately upon notice of any claims or lawsuits brought by the participants or their relatives.

8.10 **End of Trial**

Regular Trial Termination

The end of the trial is defined as the last visit of the last subject included in the trial. Within 90 days of the end of the trial, the Sponsor/CRO will notify the Competent Authority and the Ethics Committee of the regular termination of the study as required according to national law and regulations.

Premature Trial Termination

For safety reasons, this trial may be terminated prematurely at any time by the sponsor, the Principal investigator or competent authorities. If the sponsor decides to terminate the trial for any reason, including or administrative reasons, the investigator, ethics committee and competent authority will be informed about the reason(s) for stopping the study.

8.11 **Study Report**

A clinical study report (CSR) will be prepared covering clinical and statistical aspects and summarising all findings of the clinical study. The content must be treated as strictly confidential. The study report will be sent to the Investigators, the Competent Authorities and Ethics Committees according to local requirements.

8.12 **Publication and Data Rights**

Study results, positive as well as inconclusive will be made publicly available at www.clinicaltrials.gov and www.clinicaltrialsregister.eu.

The Sponsor recognizes the traditional freedom of scientists to publish and present promptly the results of their studies and the Sponsor is committed to present or publish the results of this study, both if the results are positive, negative, or inconclusive. The presented or published data should be done using clean, checked, and validated data only, to ensure the accuracy of the results.

The Investigator shall provide any and all disclosures (including, without limitation, manuscripts, abstracts, poster presentations, any public disclosure by lecture, seminar, thesis, patent application or other means) to the Sponsor for reviewing and commenting at least sixty (60) days before planned publication. All proposed disclosures shall be in final form such that the Sponsor can review the proposed disclosure in completion and in context. Any information identified by the Sponsor as confidential must be deleted prior to submission.

The Sponsor may require any proposed disclosure to be delayed for up to 3 months to enable a patent application to be prepared and filed.

Published research material shall acknowledge the assistance and contribution of the involved parties in accordance with standard academic practices, including acknowledgement via co-authorship where appropriate.

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10 SUMMARY OF PROTOCOL AMENDMENTS

Protocol version	Includes amendment no.	Main changes
1.0	Not applicable	Not applicable
2.0	01	[redacted]
3.0	2.0	[redacted]
3.1	Non substantial changes	[redacted]
3.2	Non substantial changes	[redacted]

		[redacted]

11 SIGNATURES

The protocol has been approved by:

Name and function	Signature	Date
[redacted] Senior Medical Monitor		
[redacted] Head of Clinical Development and Operations		
[redacted] Coordinating Investigator		

12 SIGNATURE PAGE FOR INVESTIGATOR

By signing this page, the Investigator confirms having read the entire protocol and its appendices and agrees to conduct this study in accordance with the protocol, GCP, the Declaration of Helsinki, Clinical Trials Regulation EU No 536/2014 and national regulations.

The signature also confirms that the Investigator agrees that the results of this study may be used for submission to national and/or international registration and supervising authorities. The authorities will be notified of the Investigators name, address, qualifications and extent of involvement.

Name	**Signature**	**Date**

13 APPENDICES

A. Numerical Rating scale for pain intensity ratings
B. Wong-Baker Faces scale
C. FLACC scale
D. Sedation scoring – university of Michigan Sedation Score
E. Treatment satisfaction

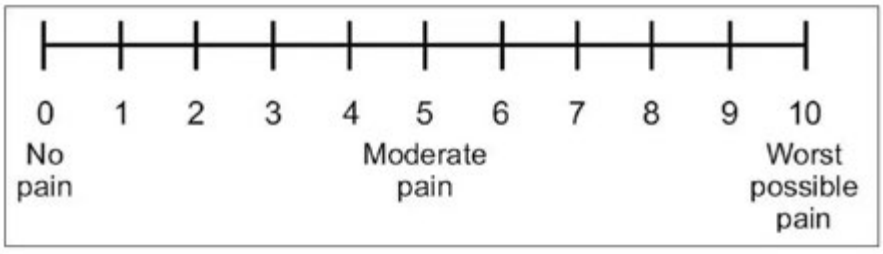
Appendix A

Numerical Rating Scale for Pain

Patient no:_____

Date:_____ Time:_____

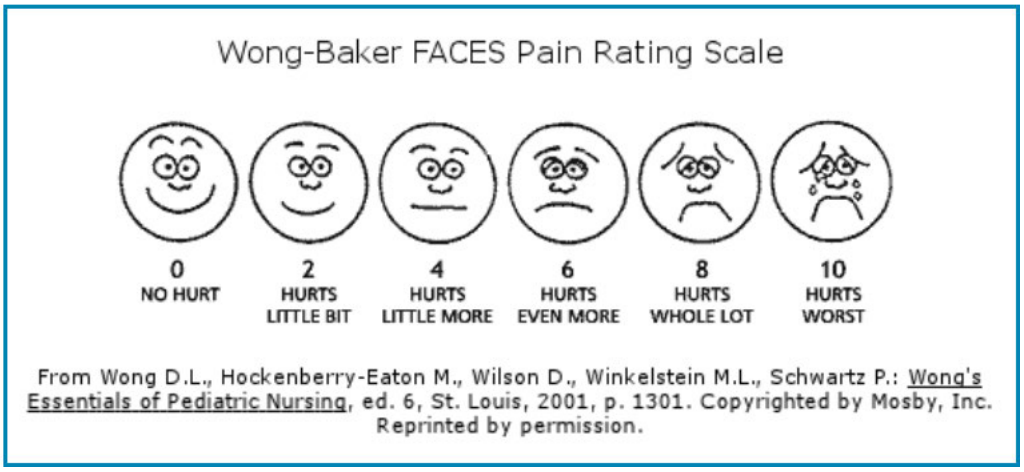
Children older than 8 years will be able to self-report pain with the use of a Numerical Rating Scale (NRS) (Area: 0-10, where 0 is not pain and 10 is worst possible pain)



NRS score: _____

Appendix B

Wong-Baker scale for self-rating of pain in verbal children ≥ 5 up to 9 years old.



From Wong D.L., Hockenberry-Eaton M., Wilson D., Winkelstein M.L., Schwartz P.: Wong's Essentials of Pediatric Nursing, ed. 6, St. Louis, 2001, p. 1301. Copyrighted by Mosby, Inc. Reprinted by permission.

Appendix C

FLACC (Face, Legs, Activity, Cry, Consolability) scale

Patient no:_____
Date:_____ Time:_____

For assessment of pain in children 1-4 years the FLACC (Face, Legs, Activity, Cry, Consolability) - score should be used. The scale is scored in a range of 0–10 with 0 representing no pain. The scale has five criteria, which are each assigned a score of 0, 1 or 2.

Criteria	Score 0	Score 1	Score 2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, uninterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting, back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractable	Difficult to console or comfort

Extracted from *The FLACC: A behavioral scale for scoring postoperative pain in young children*, by S Merkel and others, 1997, Pediatr Nurs 23(3), p. 293–297)

How to use the FLACC-scale:

1. The child should be evaluated for each of the 5 categories and each of the categories should be scored from 0-2.
2. Add the score from each of the 5 categories to give a total score of 0-10.
3. Document the total pain score.

FLACC pain score: _____

Appendix D

Michigan University Sedation Scale

University of Michigan Sedation Scale (UMSS)	
0	Awake and alert
1	Minimally sedated: tired/sleepy, appropriate response to verbal conversation and/or sound
2	Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated: deep sleep, arousable only with significant physical stimulation
4	Unarousable

S. Malviya* , T. Voepel-Lewis, A. R. Tait, S. Merkel, K. Tremper and N. Naughton. Depth of sedation in children undergoing computed tomography: validity and reliability of the University of Michigan Sedation Scale (UMSS) British Journal of Anaesthesia 88 (2): 241±5 (2002)

Appendix E

Treatment Satisfaction

Patient no:_____ Date:_____ Time:_____

How satisfied are you with the study drug that you/your child received? Please think about how it helped their pain, how it was given, any side effects, and how quickly you/your child recovered.

				
Very unsatisfied	**Unsatisfied**	**Neutral**	**Satisfied**	Very **satisfied**
1	**2**	**3**	**4**	**5**