A Comparative, Randomized, Double-blind, 3-arm parallel, Phase III Study to Evaluate the Efficacy and Safety of a Fixed Dose Combination of Nefopam/Paracetamol (tablet) Taken Orally in Moderate to Severe Pain After Impacted Third Molar Extraction

METAPAIN

Clinical study protocol: UP-CLI-2019-002

Version 1.0 – 23 July 2020

Sponsor	**UNITHER Pharmaceuticals** 3-5 Rue Saint-Georges 75009 Paris France
Test product	30 mg nefopam hydrochloride / 500 mg paracetamol Fixed Dose Combination (FDC) (Compound number: 08P1737F0)
Development Phase	III
EudraCT number	2020-002245-42
International Study Coordinator	**Professor Thomas Dietrich** Professor of Oral Surgery The School of Dentistry - University of Birmingham 5 Mill Pool Way B5 7EG United Kingdom
Contract Research Organisation	**EXCELYA Bordeaux** 7 Rue Pierre Mendès France Bât. C 33270 Floirac - France

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

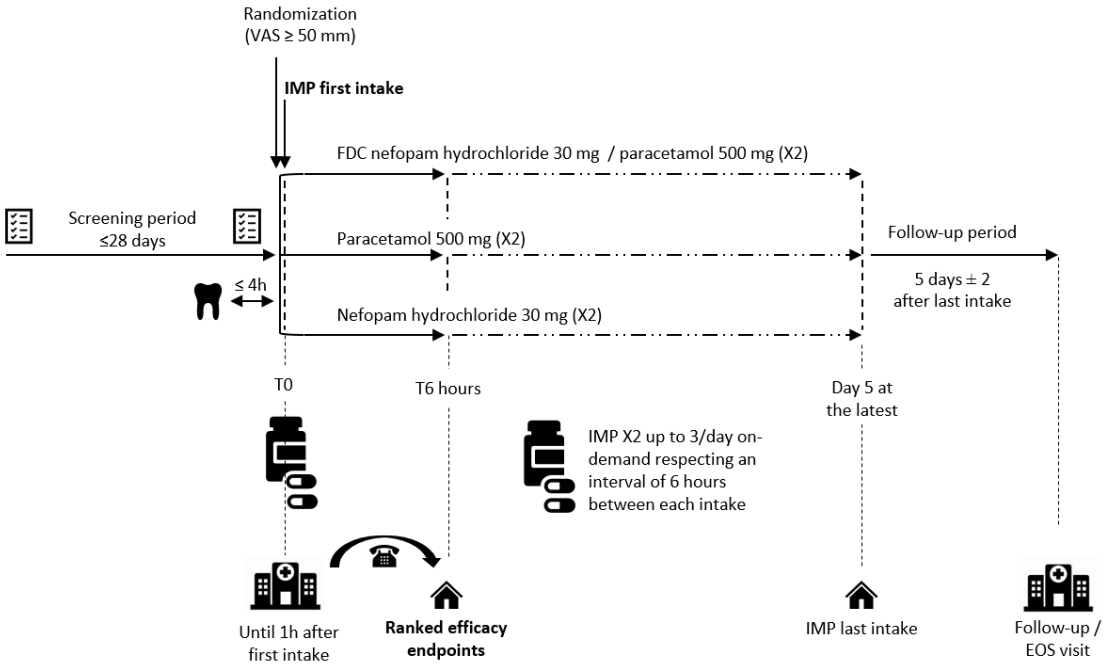
PROTOCOL AMENDMENTS: SUMMARY OF CHANGES

Version number	Date	Changes from previous version
1.0	23/07/2020	Initial version

SYNOPSIS

COMPOUND: 08P1737F0	STUDY N°: UP-CLI-2019-002 STUDY NAME: METAPAIN

STUDY TITLE	A Comparative, Randomized, Double-blind, 3-arm parallel, Phase III Study to Evaluate the Efficacy and Safety of a Fixed Dose Combination of Nefopam/Paracetamol (tablet) Taken Orally in Moderate to Severe Pain After Impacted Third Molar Extraction
SPONSOR	UNITHER Pharmaceuticals 3-5 Rue Saint-Georges 75009 Paris France
PHASE	III
INDICATION	Symptomatic short-term treatment of moderate to severe somatic pain
STUDY COORDINATOR	Prof. Thomas DIETRICH, Professor of Oral Surgery The School of Dentistry - University of Birmingham 5 Mill Pool Way B5 7EG United Kingdom
INVESTIGATIONAL SITES	International Multicentre study Around 25 sites in Belgium, France, United Kingdom and Russia
STUDY TIMELINES	First Patient In (FPI): November 2020 Last Patient Out (LPO): July 2021
STUDY DESIGN	A phase III, interventional, international, multicentre, randomized, repeated dose, double blind, 3-arm parallel groups, comparative study in patients with moderate to severe pain after impacted third molar extraction. The patients will be randomized in a 1:1:1 ratio to one of the 3 treatment groups: 1. FDC nefopam hydrochloride 30 mg / paracetamol 500 mg (x2) 2. Paracetamol 500 mg (x2) 3. Nefopam hydrochloride 30 mg (x2)



NUMBER OF PATIENTS	About 401 patients will be screened in order to reach a total of 321 patients randomized (80 screen failures are anticipated) in the trial to ensure 255 evaluable patients. A patient will be considered evaluable if he/she has an assessment of the first ranked endpoint after the first Investigational Medicinal Product (IMP) intake (drop-out 20%).
PATIENT INCLUSION CRITERIA	**Inclusion criteria:** A patient will be eligible for inclusion in this study only if all the following criteria are met: 1. Male and female patient aged from 18 years up to 65 years at the time of signing the informed consent, 2. Patient scheduled to undergo the surgical removal of at least one fully or partially impacted third mandibular molar requiring bone removal under short-acting local anaesthetic (mepivacaine or lidocaine) with or without vasoconstrictor, [redacted].

Exclusion criteria:

Patients with the following criteria will be considered not eligible to enter in the study:

1. Patient treated by analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs) within 3 days preceding the day of randomization or within 5 times the elimination half-life whichever the longest,
2. Woman with positive results on a urine pregnancy test or breastfeeding woman or woman of childbearing potential without an effective contraception,
3. Patient with a history of convulsive disorders,
4. Patient taking mono-amine-oxidase (MAO) inhibitors (including but not limited to selegiline, isocarboxazid, tranylcypromine, phenelzine…),
5. Patient with an abnormal cardiac condition: medically significant disorders of cardiac rate and/or rhythm,
6. [redacted]

INVESTIGATIONAL MEDICINAL PRODUCTS	**Investigational Medicinal Products (IMP)** Test Product: - FDC 08P1737F0: nefopam hydrochloride 30 mg / paracetamol 500 mg tablet *per os* (x2) included in a masking capsule Comparators: - Paracetamol 500 mg *per os* (Panadol® 500 mg tablet) (x2) included in a masking capsule - Nefopam hydrochloride 30 mg *per os* (Acupan® 30 mg tablet) (x2) included in a masking capsule **Dose regimen** The IMP intake should be 2 capsules at each administration. A first IMP intake is mandatory at T0 (within 4 hours after surgery), then on-demand respecting a 6-hour interval between intakes, and up to 3 intakes per day during the rest of the study.
AUXILIARY PRODUCT	**Non-Investigational Medical Product (NIMP) used as rescue medication:** Rescue Medication [redacted].
STUDY OBJECTIVES	**Ranked efficacy objectives:** To evaluate, after one single administration, the efficacy of nefopam hydrochloride (30 mg) / paracetamol (500 mg) x2 oral Fixed Dose Combination (FDC) versus oral nefopam hydrochloride alone (30 mg) x2 and oral paracetamol alone (500 mg) x2 in patients with moderate to severe pain after impacted third mandibular molar extraction on: 1. the pain intensity reduction at 6 hours ($SPID_{0-6h}$) 2. the total pain relief at 6 hours ($TOTPAR_{0-6h}$) 3. the number and proportion of responder patients at 6 hours 4. the patient's global evaluation of the treatment at 6 hours 5. the onset of pain relief **Exploratory efficacy objectives:** Other efficacy objectives of the study are to assess the efficacy of nefopam hydrochloride (30 mg) / paracetamol (500 mg) x2 oral Fixed Dose Combination (FDC) versus oral nefopam hydrochloride alone (30 mg) x2 and oral paracetamol alone (500 mg) x2 after single or multiple administrations on: - The total pain relief (assessed with TOTPAR) at 1h, 2h, 3h and 4h - The pain intensity reduction after a single dose period (assessed with SPID at 1h, 2h, 3h and 4h, and assessed with pain intensity difference (PID) at T30, T45, T60, T90, T120, T150, T180, T240, T300, T360 min) - The number and proportion of responder patients at 1h, 2h, 3h and 4h - The duration of pain relief (assessed with the time to intake of second IMP dose and/or the time to the rescue medication intake)

- The pain intensity reduction after multidose period (assessed with SPID at days 1, 2, 3, 4 and 5)
- The use of rescue medication (Assessed with the number and proportion of patients having taken a rescue analgesic treatment throughout the study, the total dose of rescue medication taken and the mean duration under rescue medication over the 5 days)
- The drug quantity taken throughout the study
- Patient's global evaluation of the treatment at end of study or at time of first intake of rescue medication (whichever happens first)

Safety objective

To compare the safety profile of the FDC with that of the respective individual active substances.

ENDPOINTS

Ranked efficacy endpoints:

1. **Sum of Pain Intensity Differences at 6 hours ($SPID_{0-6h}$)** following the first IMP intake.

   $SPID_{0-6h}$: time-weighted summary measure of the total area under the pain intensity difference (PID) curve that integrates serial assessments of pain during the first 6 hours after the first IMP intake.

   [redacted]

2. **Total Pain Relief at 6 hours ($TOTPAR_{0-6h}$)** following the first IMP intake, measured with a 5-point verbal rating scale (VRS) (0= none – 1= a little – 2= some – 3= a lot – 4= complete pain relief).

   [redacted]

   [redacted]

3. **Number and proportion of responder patients** at 6 hours following the first IMP intake.

   A responder patient is a subject who achieves a reduction of 50% of pain intensity compared to baseline.

4. **The Patient's Global Impression of Change (PGIC) questionnaire** assessed at 6 hours after the first IMP intake or at time of first intake of rescue medication (whichever happens first).

5. **The onset of pain relief,** defined as the time to reach a pain intensity score ≤ 30 mm on a 100-mm pain intensity VAS during the first 6 hours after the first IMP intake.

   [redacted]

Exploratory efficacy endpoints:

- **Total Pain Relief** at 1 hour ($TOTPAR_{0-1h}$), 2 hours ($TOTPAR_{0-2h}$), 3 hours ($TOTPAR_{0-3h}$), and 4 hours ($TOTPAR_{0-4h}$) following the first IMP intake, measured with a 5-point verbal rating scale (0= none – 1= a little – 2= some – 3= a lot – 4= complete pain relief).

TOTPAR: time-weighted summed measure of the total area under the PAR curve that integrates serial assessments of pain during the first 1 hour, 2 hours, 3 hours and then 4 hours after the first IMP intake.

[redacted]

- **Sum of Pain Intensity Differences** at 1 hour ($SPID_{0-1h}$), 2 hours ($SPID_{0-2h}$), 3 hours ($SPID_{0-3h}$), and 4 hours ($SPID_{0-4h}$)

[redacted]

- **The Pain Intensity Differences (PID)** assessment at the following time-points: at T30, T45, T60, T90, T120, T150, T180, T240, T300 and T360 min post-dose from the pre-dose value.

[redacted]

- **Number and proportion of responder patients** at 1 hour, 2 hours, 3 hours and 4 hours.

  A responder patient is a subject who achieves a reduction of 50% of the pain intensity compared to baseline.

- **Time to the second IMP intake**

- **Time to rescue medication intake**

- **Sum of Pain Intensity Differences (SPID)** at days 1, 2, 3, 4 and 5 ($SPID_{0-24h}$, $SPID_{0-48h}$, $SPID_{0-72h}$, $SPID_{0-96h}$, $SPID_{0-120h}$).

[redacted]

- **Number and proportion of patients having taken a rescue analgesic treatment** throughout the study.

- **The total dose of rescue medication taken.**

- **Mean duration under rescue medication over the 5 days.**

- **Number of IMP intakes throughout the study.**

	- **Patient's Global Impression of Change (PGIC)** score at end-of-study visit or at time of first intake of rescue medication (whichever happens first). **Safety endpoints:** - Occurrence and severity of adverse events (serious and non-serious adverse events). - Number of patients withdrawn from the study due to an adverse event occurrence.
STUDY PERIODS	**Screening:** For each patient, the screening period will start from signature of informed consent and end within the 4 hours qualification post-surgery. The screening evaluation should be performed, and their results checked by the Investigator within a period of 28 days before first IMP intake. Duration of screening: a maximum of 28 days. **Baseline:** Baseline data will be obtained after molar surgery right before randomization. **Inclusion:** A patient will be considered included once he/she is eligible to be randomized. **Treatment:** The patients who meet all eligibility criteria (including additional inclusion criteria after surgery) will be randomized. Randomized patients will receive two capsules of IMP at T0, then, respecting at least a 6-hour period between each intake, the patients will be allowed to take, on-demand, 2 capsules of IMP up to 3 times per day until day 5. Maximal total duration of treatment: 5 days. [redacted] **Follow-up:** Patients will be followed 5 days (±2) after the last IMP intake including a tolerance follow-up (for both IMP and/or rescue medication). At the end of the follow-up period, patients will undergo an end of study (EOS) visit. In the event of premature discontinuation or patient withdrawal from the study, an EOS visit will be performed within 5 days (±2) if possible.
STUDY DURATION	Maximal duration for each patient from screening to end of follow-up: 40 days The total length of the study, from screening of the first patient to the end of the study, is expected to be 9 months.
STUDY DISCONTINUATION	The reason for premature IMP discontinuation / study withdrawal should be accurately assessed and entered into the electronic Case Report Form (eCRF).
STATISTICAL METHODS	**Sample size** The sample size is based on 2 superiority statistical tests. Each t-test is performed at a two-sided type-I risk of 5%. The type-II risk is fixed to 10% (statistical power of 90%). With a design arm ratio 1:1:1 and a standardized effect size of 0.5, this yields to a sample size of 85 participants by treatment arm. Assuming a drop out of 20%, a total of 321 subjects will be randomized in the trial, i.e. 107 per arm.

General considerations:
The following descriptive analysis will be performed overall, by treatment arm and stratification group (pain at baseline):

- For quantitative variables: number of analyzed values, number of missing values, mean, standard deviation, minimum, maximum, median and interquartile range. When relevant, confidence intervals will be calculated for the mean or median.
- For qualitative variables: number of analyzed values, number of missing values, number and percentage of observations in each category of variable. When relevant, confidence intervals of proportions will be calculated.

[redacted]

Populations:
Analyses will be performed on the following population:

- Full Analysis Set (FAS) population
- Per Protocol (PP) population
- Safety population

Statistical analysis:
The efficacy analysis is based on the following ranked efficacy endpoints:

1. Sum of Pain Intensity Differences at 6 hours ($SPID_{0-6h}$)
2. Total Pain Relief at 6 hours ($TOTPAR_{0-6h}$)
3. Number and proportion of responder participants at 6 hours
4. The Patient's Global Impression of Change (PGIC) questionnaire at 6 hours
5. The onset of pain relief

[redacted]

Missing data handling:

- [redacted]

Exploratory analysis:

- Total Pain Relief at 1 hour, 2 hours, 3 hours and 4 hours.
- Sum of Pain Intensity Differences after a single dose period at 1 hour, 2 hours, 3 hours and 4 hours.
- The Pain Intensity Differences (PID) at T30, T45, T60, T90, T120, T150, T180, T240, T300 and T360 min post-dose from the baseline value.
- Number and proportion of responder patients at 1 hour, 2 hours, 3 hours and 4 hours.
- Time to the second IMP intake.
- Time to the rescue medication intake.
- Sum of Pain Intensity Differences (SPID) after a multidose period at days 1, 2, 3, 4 and 5.
- Number and proportion of patients having taken a rescue analgesic treatment throughout the study.
- The total dose of rescue medication taken.
- Mean duration under rescue medication over the 5 days.
- Number of IMP intakes throughout the study.
- Patient's Global Impression of Change (PGIC) score at end of study or at time of first rescue medication intake (whichever happens first).

Safety analysis

The safety analysis will be performed on the safety population and described overall, by treatment arm and by group of pain at baseline using descriptive statistics.

Schedule of Assessments

Procedures	Screening (Day-28 to Day1)	Inclusion (Day 1 – at study site)	During the first 6 hours post IMP (Patient out of site)	During the on-demand period (after 6 hours post IMP)	End of Study Visit
[redacted]	[redacted]				
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]				
[redacted]	[redacted]	[redacted]			
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[redacted]				[redacted]	
[redacted]	[redacted]				[redacted]
[redacted]					[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]

LIST OF ABBREVIATIONS

ANSM	Agence Nationale de sécurité du médicament et des produits de Santé
ADR	Adverse Drug Reaction
AE	Adverse Event
AUC	Area Under the Curve
CA	Competent Authority
CDISC	Clinical Data Interchange Standards Consortium
CTCAE	Common Terminology Criteria for Adverse Events
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CRO	Contract Research Organization
DIPM	Dental Impaction Pain Model
DSMB	Data Safety Monitoring Board
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
e-diary	electronic Diary
EMA	European Medicines Agency
EOS	End Of Study
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
FPI	First Patient In
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board

IV	Intravenous
IWRS	Interactive Web Response System
LPO	Last Patient Out
LS	Least Square
MAA	Marketing Authorization Application
MAO	Mono-amine oxidase
NIMP	Non-Investigational Medicinal Product
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
PAR	Pain Relief
PGIC	Patient Global Impression of Change
PID	Pain Intensity Difference
PP	Per Protocol
PRO	Patient Reported Outcome
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SMF	Site Master File
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPID	Sum of Pain Intensity Difference
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TOTPAR	Total Pain Relief
UADR	Unexpected Adverse Drug Reaction
UK	United Kingdom
VAS	Visual Analog Scale
VRS	Verbal Rating Scale
WHO	World Health Organization
WOCF	Worst Observation Carried Forward

TABLE OF CONTENT

1 INTRODUCTION AND RATIONALE

1.1 Disease and context

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. Pain is a major health problem that substantially alters quality of life. Treatment of pain is a challenge in clinical practice as not all patients respond sufficiently to available treatments and the burden of adverse reactions may be high. It is a complex process involving interactions between peripheral and central nervous system pathways with various neurobiological mechanisms being involved. Pain is always subjective and remains the leading cause of physician consultations.

[redacted]

1.2 Treatment of pain

The World Health Organization (WHO) created – initially for cancer pain relief in adults - a three-step ladder ("pain ladder" or analgesic ladder) [3]. This ladder, proposing therapeutic strategy in pain control, is now widely used by medical professionals as a guideline for the use of drugs in the management of all types of pain.

The WHO's therapeutic strategy relies upon the concurrent and sequential use of a series of treatment procedures, which must be adapted to the needs of the individual patient. For patients with mild pain, the recommendation is to use a non-opioid drug, such as aspirin, paracetamol, or any of the non-steroidal anti-inflammatory drugs. If, in the recommended dosage and frequency, this is not effective

[redacted]

[redacted]

[redacted]

[redacted]

1.3 Rational for nefopam/paracetamol as a Fixed Dose Combination (FDC)

Nefopam and paracetamol are two analgesic drugs from different pharmacological classes.

[redacted]

[redacted]

[redacted]

[redacted]

1.4 Non-Clinical and Clinical Information

1.4.1 Non-clinical development

Non-clinical safety studies were performed in accordance with Good Laboratory Practice. For more information, refer to the Investigator's Brochure.

1.4.2 Clinical development

[redacted]

1.5 Rationale of the study

[redacted]

The guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017) [9] indicates that a randomized controlled trial should be conducted to demonstrate that the fixed combination medicinal product has a:

1) superior efficacy on a clinical outcome at a given time point, AND

2) an acceptable safety profile compared with the respective individual active substances.

[redacted].

2 STUDY OBJECTIVES

2.1 Ranked efficacy objectives

The ranked efficacy objectives are to evaluate, after one single administration, the efficacy of nefopam hydrochloride (30 mg)/paracetamol (500 mg) x2 oral FDC versus oral nefopam hydrochloride alone (30 mg) x2 and oral paracetamol alone (500 mg) x2 in patients with moderate to severe pain after impacted third molar mandibular extraction, on:

1. the pain intensity reduction at 6 hours ($SPID_{0\text{-}6h}$)
2. the total pain relief at 6 hours ($TOTPAR_{0\text{-}6h}$)
3. the number and the proportion of responder patients at 6 hours
4. the patient's global evaluation of the treatment at 6 hours
5. the onset of pain relief

2.2 Exploratory efficacy objectives

The exploratory efficacy objectives are to assess the efficacy of nefopam hydrochloride (30 mg) / paracetamol (500 mg) x2 oral FDC versus oral nefopam hydrochloride alone (30 mg) x2 and oral paracetamol alone (500 mg) x2 after single or multiple administrations of the FDC:

- Total Pain Relief (assessed with TOTPAR) at 1h, 2h, 3h and 4h
- The pain intensity reduction after a single dose period (assessed with SPID at 1h, 2h, 3h and 4h, and assessed with the Pain Intensity Difference (PID) at T30, T45, T60, T90, T120, T150, T180, T240, T300 and T360 min)
- Number and proportion of responder patients at 1h, 2h, 3h and 4h
- Duration of pain relief (assessed with the time to intake of second IMP dose and/or the time to the rescue medication intake)
- The pain intensity reduction after the multidose period (assessed with SPID at Day 1, 2, 3, 4 and 5)
- The use of rescue medication (Assessed with the number and proportion of patients having taken a rescue analgesic treatment throughout the study, the total dose of rescue medication taken and the mean duration under rescue medication over the 5 days)
- The drug quantity taken throughout the study
- Patient's global evaluation of the treatment at end of study visit or at time of first intake of rescue medication (whichever happens first)

2.3 Safety objective

To compare the safety profile of the FDC with that of the respective individual active substances.

3 SELECTION OF STUDY POPULATION

3.1 Number of patients

About 401 patients will be screened in order to reach a total of 321 patients randomized (80 screen failures are anticipated) in the trial to ensure 255 evaluable patients. A patient will be considered evaluable if he/she has an assessment of the first ranked endpoint after the first IMP intake (drop-out 20%).

The patients will be randomized in a 1:1:1 ratio to one of the 3 treatment groups:

1. FDC nefopam hydrochloride 30 mg / paracetamol 500 mg (x2)
2. Paracetamol 500 mg (x2)
3. Nefopam hydrochloride 30 mg (x2)

3.2 Inclusion criteria

Before any study-related procedure is undertaken, written informed consent must be obtained.

A patient will be eligible for inclusion in this study only if all the following criteria are met:

I1) Male and female patient aged from 18 years up to 65 years at the time of signing the informed consent,

I2) Patient scheduled to undergo the surgical removal of at least one fully or partially impacted third mandibular molar requiring bone removal under short-acting local anaesthetic (mepivacaine or lidocaine) with or without vasoconstrictor,

I3) [redacted]

[redacted]

3.3 Exclusion criteria

Patients with the following criteria will be considered as not eligible to enter in the study:

E1) Patient treated by analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs) within the 3 days prior to the day of randomization or within 5 times the elimination half-life whichever the longest,

E2) Woman with positive result on a urine pregnancy test or breastfeeding woman or woman of childbearing potential without an effective contraception,

[redacted]

[redacted]

4 TRIAL CONDUCT

4.1 Study design

This is a comparative, randomized, double-blind, 3-arm parallel, phase III study to evaluate the efficacy and safety of an FDC of nefopam hydrochloride / paracetamol (tablet) taken orally in patients with moderate to severe pain after impacted third molar extraction.

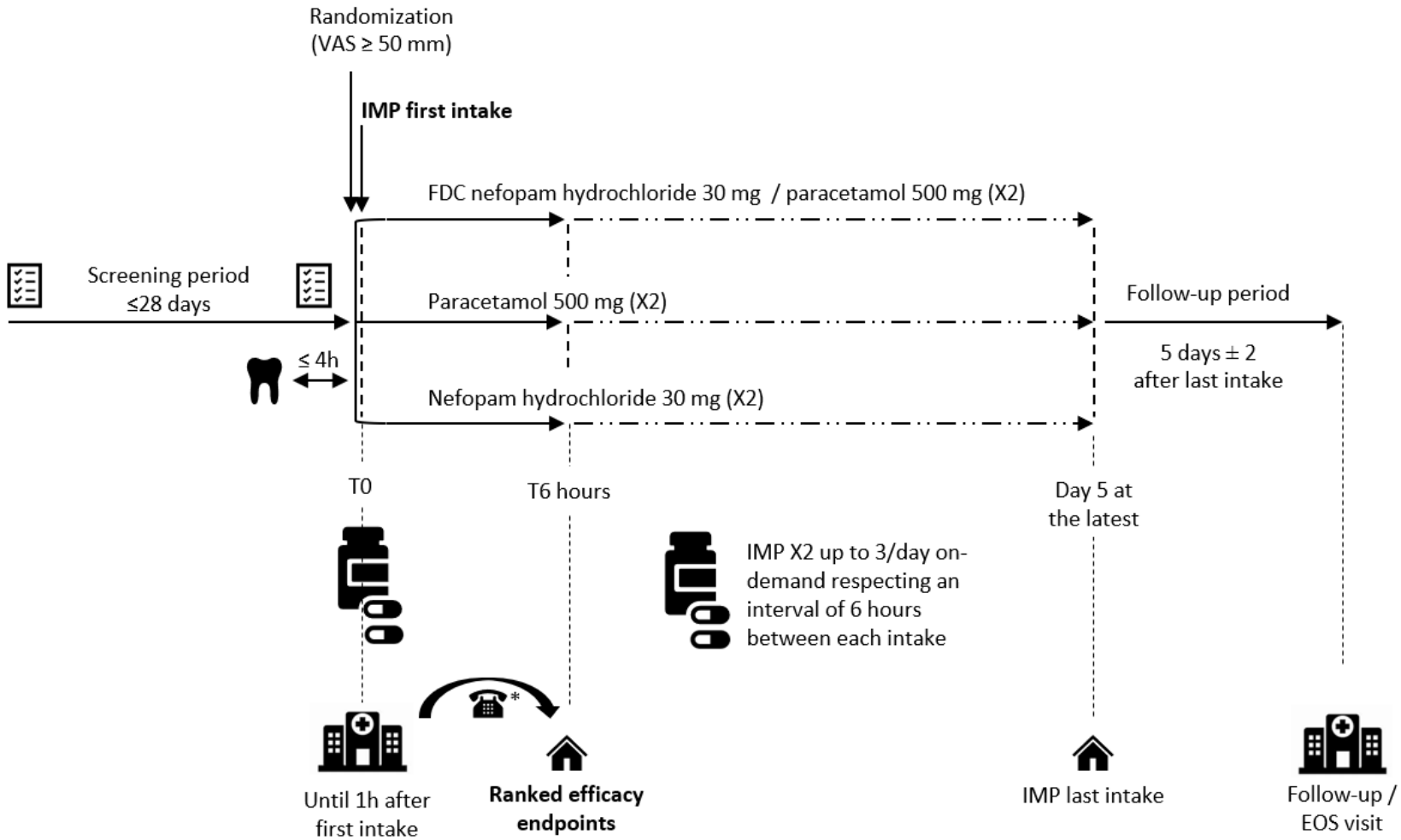
Patients will be randomized after the surgical removal of at least one impacted third mandibular molar requiring bone removal if they evaluate the pain ≥50 mm on a 100-mm VAS in a 1:1:1 ratio to one of the 3-arms:

- FDC Nefopam hydrochloride (30 mg)/paracetamol (500 mg) (x2)
- Paracetamol (500 mg) (x2)
- Nefopam hydrochloride (30 mg) (x2)

Patients will receive the first dose of investigational medicinal product (IMP) within four hours after the end of surgery (time of last suture), as soon as they reach a VAS score ≥ 50 mm. After 6 hours, the patient will take other IMPs on-demand, respecting a 6-hour interval between each intake, and limited to 3 times a day on a maximal period of 5 days.

The patients will attend an end of study visit 5 (±2) days after the last IMP intake.

4.2 Schema



* After patient discharge, one hour after IMP first intake, the Investigational site will call the patient at the time points T90, T120, T150, T180, T240, T300, T360 min to remind him/her to complete de VAS and the VRS.

4.3 Study general assessment schedule

Procedures	Screening (Day-28 to Day1)	Inclusion (Day 1 – at study site)	During the first 6 hours post IMP (Patient out of site)	During the on-demand period (after 6 hours post IMP)	End of Study Visit
[redacted]	■				
[redacted]	■	■			
[redacted]	■				
[redacted]	■				
[redacted]	■				
[redacted]		■			
[redacted]		■			
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[redacted]	■				■
[redacted]					■
[redacted]	■	■	■	■	■
[redacted]		■	■	■	■

4.4 Study assessments

4.4.1 100-mm Visual Analog Scale (VAS) for Pain Intensity

The paper visual analog scale (VAS) is a pain rating scale first used by Hayes and Patterson in 1921[10-11]. Scores are based on self-reported measure of symptoms recorded with a single handwritten mark placed at one point along the length of a 100-mm line that represents a continuum between the two ends of the scale—"no pain" on the left end of the scale (0 mm) and the "worst pain" on the right end of the scale (100 mm) (see appendix 17.1).

[redacted]

4.4.2 5-point Verbal Rating Scale (VRS) for Pain Relief

[redacted]

4.4.3 Patient's Global Impression of Change (PGIC)

[redacted]

In this study, the patients will complete the PGIC questionnaire, on their patient diary, 6 hours after the first IMP intake and at the EOS visit 5 (±2) days after the last IMP intake or at time of first intake of rescue medication (whichever happens first).

During the EOS visit, the investigator will report the results of each completed questionnaire in the eCRF.

4.4.4 Safety parameters

During the presence of the patient at study site, adverse events will be first collected by the investigator on the patient's medical file. He/she (or his/her medical staff) will, secondarily, report them on the eCRF. After leaving the study site, the patient will continue to report any new adverse event on his/her diary. The investigator will report all these new AEs from the patient diary to the eCRF during the EOS visit.

4.5 Recruitment procedure

[redacted]

4.6 Study periods

4.6.1 Screening period (from Day -28 until Day 1)

Patients presenting at an investigational dental department for at least one impacted third mandibular molar extraction will receive from the investigator an information letter and a complete explanation of the study. If the patient agrees to participate in accordance to the research requirements, he/she will date and sign an informed consent form.

After informed consent form signature, the investigator will:

- Attribute an identification number to the patient in the chronological order,
- Collect and record the patient demographic data (age, gender),
- Collect and record medical and surgical history and associated pathologies,
- Collect and record relevant treatments taken in the 30 days prior to the randomization,
- Collect the patient body weight,
- Check if the patient meets all the inclusion/exclusion criteria,
- Provide the patient with a paper diary to collect the pain intensity, the PGIC score, the adverse events and the medication intakes during the study period.
- Explain to the patient how to complete the electronic diary for the verbal rating scale.

[redacted]

[redacted]

[redacted].

A patient will be considered as enrolled once he/she signed the Informed Consent Form (ICF).

4.6.2 Baseline (Day 1)

The following screening study procedure will be carried out the day of surgery:

- Perform an oral examination,
- Perform a urine pregnancy test of women of childbearing potential,
- Collect and record relevant treatments taken in the 30 days prior to the randomization (if the baseline visit and the screening visit are not performed on the same day),
- Check if the patient meets all the inclusion/exclusion criteria.

After third molar surgery, the investigator will check the inclusion/exclusion criteria and assess if the patient fulfils the post-surgery inclusion criteria. Patients will then be asked to rest quietly at the study site and contact the research staff when they develop moderate to severe postoperative pain. Within four hours after dental extraction, the patient will complete a 100-mm VAS for pain intensity evaluation. If the score is $\geq$ 50 mm, the patient will be randomized as described in section 4.7.1.

A patient will be considered as included once he/she is eligible to be randomized.

4.6.3 Treatment period (From Day 1 to last IMP intake, maximum Day 5)

A patient will be considered as randomized once he/she has been allocated to a study arm.

After randomization, the patients will receive two capsules of IMP at T0 (within 10 minutes after the completion of the baseline pain assessment).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

If a patient experiences excessive pain, he/she will be allowed to take, on-demand, a rescue medication (ibuprofene Arrow conseil® 400 mg immediate release tablet, respecting at least a 6-hour period between each dose, and not exceeding 1200 mg per day).

In case of rescue medication use, the patient should discontinue IMP, continue to take rescue medication on-demand and to perform the VAS evaluations during the follow-up period. He/she should call the site to program the end of study visit 5 days (±2) after the last IMP intake.

Duration of the treatment period: a maximum of 5 days.

4.6.4 Follow-up (from the last IMP intake until Day 5 (±2) after the last IMP intake)

The follow-up period will last 5 (±2) days after the last IMP intake. At the end of the follow-up period, patients will undergo an end of study (EOS) visit. In the event of premature discontinuation or patient withdrawal from the study, an EOS visit will be performed within 5 (±2) days if possible.

4.7 Measures taken to minimize / avoid bias

4.7.1 Randomization

This is a randomized, double-blind study. Randomization will be stratified by centre and by level of pain intensity at baseline. A patient randomised at inclusion with a pain intensity VAS ≥50 mm and ≤60 mm will be categorized as moderate and a patient randomised at inclusion with a pain intensity VAS >60 mm will be categorized as severe.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

4.7.2 Blinding

The double-blind will be maintained throughout the study, (except exceptional unblinding at the request of the investigator or the Sponsor). The labelling of treatment units will comply with this blinding (see Section 7.3 Packaging and Labelling).

[redacted]

In case of unblinding, the following information must be documented:

- the name and title of the person who used IWRS
- the decoding date
- the patient's number
- the reasons for unblinding

4.8 Discussion and Justification of Study Design

4.8.1 Discussion of Study Design and Choice of Control Group

The randomized clinical trial is a gold standard in clinical trial designs. This design is more likely to provide solid evidence for determining the efficacy and safety of our FDC.

[redacted]

4.8.2 Justification of selected dose in the Study

[redacted]

5 DEVIATION TO THE PROTOCOL

A deviation to the protocol is any change, divergence or gap compared to the study's conception or the protocol procedures that is under the investigator control, and that has not been approved by health authorities.

The following items will be considered as deviations to the protocol (non-exhaustive list):

- Wrong inclusion according to the inclusion/exclusion criteria (cf. sections 3.2, 3.3 and 3.4),
- Intake of forbidden treatments
- Study schedule not respected
- Bad compliance

[redacted]

6 DURATION OF THE STUDY

6.1 Chronology and duration of the different steps

[redacted]

6.2 Duration of patient participation

The duration for each patient from screening to follow-up will be a maximum of 40 days.

6.3 Withdrawal of individual subjects

6.3.1 Premature withdrawal

Patients have the right to withdraw from the study at any time for any reason, without prejudice by withdrawing their consent without the need to justify their decision. The Investigator must withdraw from the study any patient who requests to stop participating in the study. Patients who withdraw their consent will be asked to undergo the study assessments scheduled at the EOS visit. They will be advised that participation to the EOS visit is voluntary but is in their best interest.

A patient's participation in the study can also be ended prematurely if he/she has been wrongfully included or if he/she is lost to follow-up.

[redacted]

6.3.2 End of study

The follow-up visit within 5 (±2) days after the last intake represents the normal EOS visit.

[redacted]

6.4 Study termination

6.4.1 Definition of study termination

The end of the study corresponds to the last visit of the last patient included in the study (LPLV = LPO).

Any changes in this definition during the study should be written in a protocol amendment.

6.4.2 Premature study termination

The Sponsor can terminate the trial at any time for any reason. In this case, the patients should be seen as soon as possible and treated as in the normal EOS visit (Section 6.3.2).

[redacted]

7 STUDY PRODUCTS

7.1 Test product

Denomination:	Fixed Dose Combination of nefopam hydrochloride 30 mg and paracetamol 500 mg tablet
Composition:	[redacted]
Pharmaceutical form:	[redacted]
Route of administration:	Oral use
Dosage:	2 capsules per intake, no more than 3 intakes per day, respecting a minimum interval of 6 hours between 2 intakes
Duration of treatment:	Until a maximum of 5 days

More information is available in the current Investigator's Brochure of FDC 08P1737F0. FDC (nefopam hydrochloride 30 mg and paracetamol 500 mg) is not currently approved in any country.

7.2 Comparative products

7.2.1 Comparative product 1:

[redacted]	[redacted]
[redacted]	[redacted]
Pharmaceutical form:	Tablet included in an orange Swedish masking capsule.
Route of administration:	Oral Use
Dosage:	2 capsules per intake, no more than 3 intakes per day
Duration of treatment:	Until a maximum of 5 days

More information is available in the current SmPC of Panadol®.

Panadol® paracetamol 500 mg, has been approved in many countries; the reference used in the study is BE541084 from the Belgium market. It will be used in the clinical trial in accordance with the conditions described in the SmPC.

7.2.2 Comparative product 2:

Denomination:	[redacted]
Composition:	The active substance is nefopam, present in the form of nefopam hydrochloride. Each tablet contains nefopam hydrochloride 30 mg. [redacted]
Pharmaceutical form:	White, round, biconvex tablet with the following inscription in relief and in capital letters in a triangle: A P N debossed on one side and plain on other side included in an orange Swedish masking capsule.
Route of administration:	Oral Use
Dosage:	2 capsules per intake, no more than 3 intakes per day
Duration of treatment:	Until a maximum of 5 days

More information is available in the current SmPC of Acupan®.

[redacted].

7.2.3 Auxiliary products (non-investigational medicinal product [NIMP] used as rescue medication)

Denomination:	[redacted]
Composition:	The active substance is ibuprofen. Each tablet contains ibuprofen 400 mg. [redacted]
Pharmaceutical form:	Coated tablet
Route of administration:	Oral Use
Dosage:	1 tablet per intake, no more than 3 intakes per day
Duration of treatment:	Until a maximum of 5 days

More information is available in the current SmPC of IBUPROFENE ARROW CONSEIL® 400 mg tablet.

[redacted]

7.3 Packaging and labelling

7.3.1 Packaging

The investigational medicinal products will be manufactured [redacted]

The secondary packaging is a box containing 3 blisters with 10 capsules of IMP sealed with adhesive seals.

[redacted]

7.3.2 Labelling

The content of the labels will be in accordance with the local regulatory specifications and requirements and translated into the local language when legally required.

The corresponding label to be applied on the primary packaging of IMP will contain the following information in the official language(s) of each selected country: the Sponsor's name, the protocol number, the batch number, the patient number, the treatment number, the site number, and the investigator identification.

[redacted]

The corresponding label to be applied on secondary packaging of NIMP will contain the following information in the official language of each selected country:

- The Sponsor's name and address: UNITHER Pharmaceuticals, 3-5 Rue Saint-Georges, 75009 Paris, France
- [redacted]

7.4 Shipment and IMP reception

Shipments of IMP to site will be organised [redacted]

7.5 Storage conditions

Investigators or other authorised persons are responsible for storing the investigational medicinal products in a secure and safe place with no access by unauthorized personnel in accordance with local regulations, labelling specifications, policies, and procedures.

[redacted]

7.6 Method of Assigning Patients to Treatment Groups

The test product or the comparative products will be assigned at T0 according to the randomization method presented in Section 4.7.1.

7.7 Method of administration

7.7.1 IMP

Only subjects enrolled in the study may receive investigational product, in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer investigational product.

The treatment will be taken by the patient orally.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

7.7.2 Rescue medication

In case of excessive pain, a rescue treatment will be permitted: ibuprofen immediate release formulation: ibuprofen 400 mg tablet (until 1200 mg / day) provided by Sponsor.

[redacted]

[redacted]

[redacted]

[redacted]

7.8 Product return and compliance

All subjects should be instructed to bring back all blisters (even empty) with any unused IMP or NIMP to end of study visit. A record of IMP and NIMP dispensed, taken and returned will be reported in the eCRF.

At the end of the study, there will be a final reconciliation of product shipped, product consumed, and product remaining, and treatment disposed. This reconciliation will be recorded in the site study drug log, signed and dated.

[redacted]

7.9 Recall

If an IMP batch is suspected to be defective, the Investigator and/or the Hospital Pharmacist will be immediately informed by the Sponsor or its representative.

IMP must immediately be put in quarantine and no further administration of the concerned batch(es) must be done until Sponsor's written instructions.

8 PRIOR AND CONCOMITANT MEDICATIONS

8.1 Prior medication

The term 'prior medication' refers to any medication given up to 30 days before inclusion.

A reasonable effort will be made to document any medications the subject received within 30 days prior to inclusion. All relevant prior medications taken within 30 days prior to inclusion must be recorded in the patient's medical file and documented on the appropriate pages of the eCRF.

Moreover, any prior medication taken more than 30 days prior to inclusion which is, in the opinion of the investigator, clinically relevant to the patient's condition will also be recorded.

The following medications are not allowed before randomization because they could interfere with the assessment of IMP efficacy:

- Any other investigational product administered within the last 30 days or 5 half-lives duration of the biological effect prior to screening.

- Analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs) within 3 days preceding the day of randomization,
- Patient taking mono-amine-oxidase (MAO) inhibitors (including but not limited to selegiline, isocarboxazid, tranylcypromine, phenelzine),

8.2 Concomitant medication

The term 'concomitant medication' refers to any medication that the patient receives at any time during the study, i.e. from inclusion to EOS visit. This includes the screening period, treatment period and follow-up as defined in the protocol. At EOS, the Investigator will ask the patient about any medication taken since the inclusion.

Treatments not allowed during the study are the following:

- Any other investigational product,
- Analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs) other than the rescue medication provided by Sponsor,
- Other anaesthetic than the authorized short acting local anaesthetics: mepivacaine or lidocaine, for the molar extraction,
- General anaesthesia and peri-operative anaesthesia,
- Sedation,
- [redacted]

[redacted]

[redacted]

9 Endpoints

9.1 Ranked efficacy endpoints

1. **Sum of Pain Intensity Differences at 6 hours ($SPID_{0-6h}$)** following the first Investigational Medicinal Product (IMP) intake.

   [redacted]

intake and/or right before first intake of rescue medication using a 100-mm Visual Analog Scale (VAS) compared to baseline.

2. **Total Pain Relief at 6 hours ($TOTPAR_{0-6h}$)** following the first IMP intake, measured with a 5-point verbal rating scale (0 = none – 1 = a little – 2 = some – 3 = a lot – 4 = complete pain relief).

[redacted]

3. **Number and proportion of responder patients at 6 hours** following the first IMP intake.

A responder [redacted]

4. **The Patient's Global Impression of Change (PGIC) questionnaire** assessed 6 hours after the first IMP intake or at time of first intake of rescue medication (whichever happens first).

5. **The onset of pain relief**, defined as the time to reach a pain intensity score ≤ 30 mm on a 100-mm pain intensity VAS during the first 6 hours after IMP intake.

[redacted]

9.2 Exploratory efficacy endpoints

- **Total Pain Relief** at 1 hour ($TOTPAR_{0-1h}$), 2 hours ($TOTPAR_{0-2h}$), 3 hours ($TOTPAR_{0-3h}$), and 4 hours ($TOTPAR_{0-4h}$) following the first IMP intake, measured with a 5-point verbal rating scale (0= none – 1= a little – 2= some – 3= a lot – 4= complete pain relief).

[redacted]

- **Sum of Pain Intensity Differences** at 1 hour ($SPID_{0-1h}$), 2 hours ($SPID_{0-2h}$), 3 hours ($SPID_{0-3h}$), and 4 hours ($SPID_{0-4h}$)

SPID: time-weighted summary measure of the total area under the pain intensity difference (PID) curve that integrates serial assessments of pain during the first 1 hour, 2 hours, 3 hours and then 4 hours after the first IMP intake

[redacted]

- **The Pain Intensity Differences (PID)** assessment at the following time-points: at T30, T45, T60, T90, T120, T150, T180, T240, T300 and T360 min post-dose from the pre-dose value.

  PID will be calculated using the scores of pain intensity (VAS) at each time point compared to baseline.

- **Number and proportion of responder patients** at 1 hour, 2 hours, 3 hours and 4hours.

  A responder patient is a subject who achieve a reduction of 50% of pain intensity compared to baseline.

- **Time to the second IMP intake**

- **Time to the rescue medication intake**

- **Sum of Pain Intensity Differences (SPID)** at days 2, 3, 4 and 5 (= $SPID_{0\text{-}24h}$, $SPID_{0\text{-}48h}$, $SPID_{0\text{-}72h}$, $SPID_{0\text{-}96h}$ and $SPID_{0\text{-}120h}$): time-weighted summary measure of the total area under the pain [redacted]

- **Number and proportion of patients having taken a rescue analgesic treatment** throughout the study

- **The total dose of rescue medication taken**

- **Mean duration under rescue medication over the 5 days**

- **Number of IMP intakes throughout the study**

- **Patient's Global Impression of Change** (PGIC) score at [redacted]

9.3 Safety endpoints

- **Occurrence and severity of adverse events** (serious and non-serious adverse events)
- **Number of patients withdrawn from the study** due to an adverse event occurrence.

10 SAFETY ASSESSMENT

10.1 Reference Safety Information Document

The current version of the Investigator Brochure of FDC 08P1737F0, will be the Reference Safety Information document to assess the expectedness of AEs.

FDC 08P1737F0 is currently in clinical development for the treatment of pain. Identified and potential risks associated with IMP treatment will be closely monitored throughout the clinical study. Patient safety during the clinical study is ensured by targeting the most appropriate patient population.

First administration of IMP will be performed in a hospital, clinic environment or dentist's office/practice under close supervision of the investigator or a medically qualified staff member. All adverse events and serious adverse events will be recorded during the study until Day 5 (±2) after the last IMP intake as provided through this study. Safety assessments will include the incidence, nature, and severity of (serious) adverse events graded per the NCI CTCAE v5.0.

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize these issues, are outlined in the following sections.

10.2 Benefit / Risk Information

10.2.1 Potential risks related to the IMPs

FDC 08P1737F0is an IMP which is the combination of two active ingredients. As a result, patients treated with [redacted]

Contraindications

IMPs are contraindicated in patients with a known hypersensitivity to paracetamol and / or nefopam hydrochloride or any of the other constituents.

IMP will not be given to patients with severe hepatic or renal impairment.

Nefopam is contraindicated in patients with a history of convulsive disorders and should not be given to patients taking mono-amine-oxidase (MAO) inhibitors. To minimize risk, patients with a history of convulsive disorders, or taking MAO inhibitors will be excluded.

As a result of Acupan® anticholinergic properties, Acupan® should be used with care in patients with glaucoma, prostatic hypertrophy or urinary retention and if necessary, stopped. To minimize risk, IMPs will not be used in patients with known glaucoma, prostatic hypertrophy or urinary retention.

Repeated administration of Panadol® is contraindicated in patients with anaemia, heart disease, and pulmonary disease. Patients with known anaemia, pulmonary disease or with an abnormal cardiac condition: medically significant disorders of cardiac rate and/or rhythm, will be excluded.

Special warnings and special precautions for use

Special warnings and precautions for use do not differ from those of the nefopam hydrochloride and paracetamol indicated in the SmPC of Acupan® dated Aug 2018 and the SmPC of Panadol® dated Oct 2019.

Potential risks are related to the hepatotoxicity due to paracetamol:

- use of enzyme inducers, such as barbiturates and anticonvulsants, excessive alcohol consumption,
- hepatic and / or renal impairment,
- chronic consumption of paracetamol may cause kidney failure,
- glutathione depletion – especially in patients with severe malnutrition, low body mass index, anorexics, chronic alcoholics, in case of glutathione deficiency like in septicaemia case, IMP can increase the risk of metabolic acidosis,
- elderly patients are more sensitive and more at risk of liver or kidney failure.

Potential risks will also be related to nefopam hydrochloride:

- anxiety symptoms, glaucoma, prostatic hyperplasia or urinary retention due to the moderate central adrenergic and anticholinergic activities of nefopam,
- pre-existing cardiovascular pathology (symptomatic tachycardia, myocardial infarction, heart failure) due to tachycardia effect of the product,
- hepatic and / or renal failure: it may interfere with metabolism and excretion of nefopam,
- elderly patients, due to their slow metabolism, are more sensitive to adverse effects of the central nervous system: a few cases of hallucination and confusion have been reported in this group of patients.

In order to minimize risk, patients with current or chronic history of liver disease, or known hepatic or biliary abnormalities, patients with a current or chronic history of severe renal impairment, patients having developed hypersensitivity reactions, including symptoms of asthma, rhinitis or urticaria after taking acetylsalicylic acid or other NSAIDs, patients with drug or alcohol abuse within 6 months before dosing with study medication will be excluded from the study.

Interaction

Interaction do not differ from those of the nefopam hydrochloride and paracetamol indicated in the SmPCs of Acupan® and Panadol®.

Possible interaction with paracetamol:

- administration of activated charcoal decreases the absorption of paracetamol in case of overdose,
- hepatic enzyme inducers (such as barbiturates, diphantoin) and alcohol may increase the hepatotoxicity of paracetamol,
- the half-life of chloramphenicol can be prolonged from 2-3 hours to 18-24 hours when concomitant use of paracetamol is used,
- the low binding of paracetamol to plasma proteins allows its association with anticoagulants. However, taking paracetamol for several days may increase the risk of bleeding. In this case, the regular check of the International Normalized Ratio (INR) is recommended,

- due to the risk of decreased leukocyte (leukopenia) levels when concomitant administration of paracetamol and AZT (zidovudine), simultaneous administration will only be with medical advice,
- paracetamol absorption may increase with metoclopramide and decrease with cholestyramine. Concomitant administration of diflunisal increases serum paracetamol levels. High serum paracetamol levels have been associated with hepatotoxicity.

Possible interaction with nefopam hydrochloride:

- the side effects of nefopam may be additive to those of other substances with anticholinergic or sympathomimetic activity,
- it must be taken into account that many drugs or substances can add their depressant effects of the central nervous system and contribute to decrease vigilance. These are morphine derivatives (analgesics, antitussives and substitution treatments), neuroleptics, barbiturates, benzodiazepines, anxiolytics other than benzodiazepines (eg meprobamate), hypnotics, sedative antidepressants (amitriptyline, doxepin, mianserine, mirtazapine, trimipramine), sedative H1 antihistamines, central antihypertensives and baclofen,
- nefopam may interfere with certain tests for benzodiazepines and opioids. These tests may give false positive results in patients taking nefopam,
- the intensity and incidence of adverse events increase when nefopam is co-administered with codeine, pentazocine or dextropropoxyphene,
- nefopam is extensively metabolized. But since the enzyme responsible for the biotransformation of nefopam is not known, it is not possible to anticipate potential interactions with CYP inhibitors / inducers. Caution should therefore be exercised whenever nefopam is co-administered with one of the CYP inhibitors / inducers,
- the known hepatotoxicity of paracetamol, seen in dogs that received very high doses of paracetamol, was increased when very high doses of nefopam were administered. These studies demonstrated that oral doses of 236 mg/kg/day of paracetamol and 24mg/kg/day of nefopam potentiate the hepatotoxicity of paracetamol. These doses are approximately six to eight times higher than the average human dose. Lower doses equivalent to three or four times the human dose did not cause potentiation of hepatotoxicity.

Adverse reactions with IMP

Adverse reactions expected do not differ from those of the nefopam and paracetamol.

The tables below are presented according to the MedDRA system organ classification (SOC) and Preferred Term Level.

Based on the marketed Panadol® 500 mg BE541084 and the marketed Acupan® 30 mg BE102383, the expected frequency of adverse reactions is presented in the tables below in CIOMS frequency categories:

- Very common (≥1/10);
- Common (≥1/100 to <1/10);
- Uncommon (≥1/1,000 to <1/100);
- Rare (≥1/10,000 to <1/1,000);
- Very rare (<1/10,000),

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Undesirable effects of paracetamol

	Very rare	Undetermined Frequency
Blood and lymphatic system disorders	Thrombocytopenia	In patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency: Haemolytic anaemia is not excluded
Immune system disorders	Cutaneous reactions including erythema, urticaria, angioedema and other signs of anaphylaxis, and Stevens-Johnson syndrome.	
Respiratory, thoracic and mediastinal disorders	Bronchospasm in patients sensitive to aspirin or other NSAIDs	
Hepatobiliary disorders	Hepatic dysfunction	
Skin and subcutaneous tissue disorders	Very rare cases of severe skin reactions have been reported.	

Undesirable effects of nefopam hydrochloride

	Very common	Common	Rare	Undetermined frequency
Psychiatric disorders			Excitability*,Irritability* Hallucination Abuse** Drug-dependence**	Confusionnal state
Nervous system disorders	Drowsiness	Dizziness* Light-headedness Paraesthesia Tremor	Convulsions* Confusion Postoperative confusion Insomnia Headache	Coma
Cardiac disorders		Tachycardia* Palpitations* Hypotension	Syncope	
Gastrointestinal disorders	Nausea with or without vomiting	Dry mouth* Abdominal pain Diarrhoea		
Renal and urinary disorders		Urinary retention	Decrease renal function Harmless pink discolouration of the urine	
Eye disorders			Blurred vision	
Immune system, skin and subcutaneous tissue disorders	Sweating*	Allergic reactions	Postoperative hypersensitivity (angioedema, anaphylactic shock) Pruritus Erythema Urticaria Faintness	

*Although never reported, other atropine effects than those described are likely to be observed.
**According to the PRAC conclusions, the suggested plausible mechanism is the inhibition of dopamine recapture.

Risks specific of the nefopam hydrochloride / paracetamol co-administration

In the 12 healthy volunteers which had received the oral co-administration of 30 mg nefopam hydrochloride / 500 mg paracetamol (x2), more adverse events were reported in the volunteers receiving both products. Three patients experienced AEs: nausea, sudation and diarrhoea. All the effects resolved spontaneously and rapidly. None of them conducted to any modifications in the performance of the protocol or the prescription of symptomatic treatment.

Overdose, drug abuse and dependence

Recommendations regarding overdose, drug abuse and dependence do not differ from those of the nefopam hydrochloride and paracetamol.

Related to paracetamol

In adults, a single dose of 8 to 10 g can induce liver damage. In children, the toxic dose is 120 mg / kg. The toxic dose is lower in patients with hepatic insufficiency and in patient who regularly consumes ethanol in excess of recommended amounts.

Symptoms (pallor, nausea, vomiting) usually occur in the first 12 to 24 hours, but liver damage may become apparent only 3 days after overdosage. Hospitalization is mandatory, even in case of presumed intoxication. Hepatic failure is likely when plasma levels exceed 230 micrograms / mL after 4 hours, 50 micrograms / mL after 12 hours and are still detectable after 24 hours. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage.

Immediate treatment is essential in the management of paracetamol overdose. The stomach should be emptied as quickly as possible by gastric lavage or induction of vomiting. Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. However, the main therapeutic measure consists in the intravenous administration of N-acetylcysteine at 150 mg / kg in 30 to 60 minutes, then 50 mg / kg in 4 hours, then 100 mg / kg in 16 hours. The 5% glucose volume used as an infusion fluid will be determined according to the age and weight of the patient. In case of particularly serious intoxication, the administration of N-acetylcysteine can be continued until the 48th hour. Overdosage of paracetamol may cause liver failure. In case of overdose, medical attention is immediately necessary, even if the symptoms of an overdose are not present. Administration of N-acetylcysteine or methionine may be required.

Related to nefopam

Symptoms are due to the anticholinergic effects of nefopam. The clinical pattern of nefopam toxicity in overdose is on the neurological (coma, convulsions, hallucinations) and the cardiovascular systems (tachycardia).

The first signs of toxicity, ie tachycardia, occur after taking 30 cp of nefopam hydrochloride tablets (15 mg/kg). Hospitalization is necessary at this dose.

Treatment: routine supportive measures should be taken and if the drug has been swallowed less than one hour before, a prompt removal of ingested drug by gastric lavage or induced vomiting with syrup of Ipecacuanha should be carried out. Oral administration of activated charcoal may help prevent

absorption. Convulsions and hallucinations should be controlled (eg with intravenously or rectally administered diazepam). Beta-adrenergic blockers may help control the cardiovascular complications.

Effects on ability to drive and use machine

Paracetamol has no effect on the ability to drive and use machines.

For patients who experience the central nervous side effects of nefopam, it may be unwise to drive or operate machinery.

10.2.2 Potential risks related to the NIMP: Ibuprofene Arrow Conseil® 400 mg tablet

Contraindications

This medication is contraindicated in the following situations:

- Hypersensitivity to the active substance or to any of the excipients;
- History of asthma triggered by taking ibuprofen or substances of close activity such as: other NSAIDs, acetylsalicylic acid;
- Pregnancy, from the beginning of the 6th month (beyond 24 weeks of amenorrhea);
- History of gastro-intestinal bleeding or ulcer due to previous NSAIDs treatments.
- Current evolution or recurrent ulcer / stomach bleeding
- History of stomach bleeding or digestive perforation during previous treatment with NSAIDs;
- Current gastrointestinal haemorrhage, or history of gastrointestinal haemorrhage, cerebrovascular haemorrhage or other evolving haemorrhage,
- Severe liver pathology;
- Severe kidney pathology;
- Severe heart pathology;
- Systemic lupus erythematosus.

In order to minimize risks, patients are excluded if they are:

- Women with positive results on a urine pregnancy test or breastfeeding women or women of childbearing potential without an effective contraception,
- with an abnormal cardiac condition: medically significant disorders of cardiac rate and/or rhythm,
- with known active gastric or duodenal ulcer or a history of recurrent gastrointestinal ulcer/bleeding,
- with any known hypersensitivity to nefopam, paracetamol, ibuprofen or ingredients contained in IMP and NIMP.
- with current or chronic history of liver disease, or known hepatic or biliary abnormalities,
- with a severe renal impairment (glomerular filtration below 30 mL/min),
- having developed hypersensitivity reactions, including symptoms of asthma, rhinitis or urticaria after taking acetylsalicylic acid or other NSAIDs,
- with known systemic lupus erythematosus

Undesirable effects of ibuprofene arrow conseil®400 mg

Some side effects can occur with Ibuprofene Arrow conseil® such as gastrointestinal in nature.

In rare cases, peptic ulcers, perforations or gastrointestinal bleeding, may occur.

Skin rash, asthma, angioedema, heart failure or and angina pectoris related to NSAID therapy have been reported.

For complementary information, please refer to the provided SmPC.

10.2.3 Benefit/Risk Balance

FDC 08P1737F0 is not currently approved in any country.

However, paracetamol and nefopam hydrochloride are worldwide registered and marketed since the end of the 1950s and the beginning of the 1970s respectively, with a current hospital and retail use. Moreover, co-administration of paracetamol and nefopam is currently performed in hospital setting.

The type of active substances used in this protocol is already commonly used and its efficacy has been proven. The total dose recommended in this protocol may vary from one patient to another, but it will not exceed the doses used in current practice in this indication. For all these reasons, it is judged that participation in the study does not induce significant additional risk for patients.

10.3 Definitions in relation with the vigilance

10.3.1 Adverse event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

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

10.3.2 Adverse drug reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

10.3.3 Serious adverse event or reaction (SAE or SAR)

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

[redacted]

- Hepato-biliary disorders (related to the use of paracetamol)

10.4 Recording, assessment and reporting of AE and AR, SAE and SAR

10.4.1 Recording of adverse events

Any adverse event should be recorded in the form ''adverse event'' of the eCRF.

10.4.2 Assessment of adverse events

The investigator should evaluate the following parameters for any adverse event recorded within the research:

- Intensity,
- Causality,
- Severity,
- Unexpectedness.

10.4.2.1 Assessment of intensity:

The assessment of the intensity accords with CTCAE V5.0:

Mild adverse event:
- asymptomatic or mild symptoms,
- clinical or diagnostic observations only,
- intervention not indicated.

Moderate adverse event:
- minimal, local or non-invasive intervention indicated,
- limiting age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).

Severe adverse event:
- medically significant but not immediately life-threatening,
- hospitalization or prolongation of hospitalization indicated,
- disabling,
- limiting self-care activities of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

10.4.2.2 Assessment of causality

In the eCRF form, the causality link is evaluated:
- Compared to research (act, method, related products…),
- Compared to study products (active/comparative),
- According to the criteria: excluded, not excluded.

The causality could be considered as ''excluded'', only whether:
- A clear alternative explanation exists, AND/OR,
- The event occurs according to a chronology incompatible with the time of study product intake and/or with the study conduct, AND/OR,
- The relationship between research and the event is not plausible.

The causality could be considered as "not excluded", only whether:
- The event occurs according to a chronology compatible with the time of study product intake and/or with study conduct AND/OR,
- The relation between the event and the research is plausible, but the event could also be explained by a concurrent disease or other drugs or chemicals OR,
- The event is part of adverse events expected in the context of the research.

In the SAE notification report, the causality link will be also evaluated:
- Compared to the research (without link with study products),
- Compared to study products,
- Compared to other factors to be specified,
- According to the criteria: not related, possibly, likely, certain.

[redacted]

- A clear alternative explanation exists, AND/OR,

- The event occurs according to a chronology incompatible with the time of study product intake and/or with the study conduct, AND/OR,
- The relationship between research and the event is not plausible.

10.4.2.3 Assessment of the unexpected nature

The assessment of unexpected nature of the adverse event is based on the information described in the protocol or in the technical file relating in particular, where appropriate, to acts and methods carried out during the research or products being used for the research or for the purpose of the research.

If an adverse effect concerns a health product used for the trial purposes, it is appropriate to determine the unexpected nature of this effect, to refer to the information contained in repositories in force if the product is used in accordance with these.

10.5 Notification of serious adverse event and reaction, or SUSAR

The investigator must inform Pharmacovigilance CRO (Axpharma) of any serious adverse event occurring during the research or within 15 days following end of research (via SAE notification report form (see appendix 17.5).

The notification must be done without delay from the time(s) he/she is aware of the event.

[redacted]

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

[redacted]

Information concerning the follow-up of serious adverse event should be reported by the investigator within the same deadline.

If a non-serious adverse event becomes serious, this one and any relevant follow-up information should be transmitted to the Sponsor or authorized personnel immediately, as described above.

Any suspicion of serious adverse effect already reported to the authority must be reported again in case of accentuation.

The SAE or SUSAR declaration to the Competent Authorities (CA) / IEC (independent Ethic Committee) will be done according to each country's regulations by the Sponsor or its representative.

- Without any delay for the SUSAR having caused death or life-threatening.
- Within the 15 days from the time the Sponsor has been aware of the event for the other SUSAR.

10.6 Follow-up of adverse event and reaction

The investigator will need to follow the patient until the end of his/her participation in the trial.

At the end of the participation of the patient:

- If an adverse event unrelated to the research or study products of the research is in progress, the investigator must guide the patient to his/her general practitioner, if applicable.
- If a serious adverse event is in progress, the investigator must report any evolution of the event to the Sponsor.
- If a suspicion of AR or SAR is in progress at the end of the participation of the patient, the investigator must organize his/her follow-up together with the patient's general practitioner (if applicable). This follow-up will permit to document the evolution of the event until it will be decided to close it (in case of resolution or stabilization) or until causality can be excluded.
- The Sponsor has to declare, in a follow-up report to the CA, additional relevant information concerning the unexpected SAR and SUSAR:
    - For SUSAR having caused death or life-threatening, this information will be notified within the 8 days from the declaration.
    - For other SUSAR, additional relevant information has to be notified within an additional 8 days from the declaration.

10.7 Pregnancy

Pregnancy in a study patient must be reported to [redacted] within 1 working day of the site becoming aware of the pregnancy. Patients who become pregnant during the study must be discontinued from IMP (see section 6.3)

Information regarding a pregnancy occurrence in a study patient and the outcome of the pregnancy will be collected.

Pregnancy in a study patient is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to Pharmacovigilance [redacted]

10.8 Emergency Medical Contacts

To ensure the safety of study [redacted]

The Emergency Medical Contacts will be available 24 hours per day, 7 days per week.

11 STATISTICAL CONSIDERATION

11.1 Sample size calculation

The first objective of the study is to evaluate the efficacy of nefopam hydrochloride (30 mg) / paracetamol (500 mg) x2 oral FDC versus oral nefopam hydrochloride alone (30 mg) x2 and versus oral paracetamol alone (500 mg) x2 on SPID during the first 6 hours, i.e. the 2 superiority statistical tests must be significant to conclude on the superiority of the combination.

As there is few and heterogeneous data, the sample size was based on the hypotheses that:

- the theoretical effects of individual substances on pain are the same,
- the standardized treatment effect (treatment effect divided by standard deviation) is fixed to 0.5 which corresponds to a medium effect according to Cohen (Cohen's d test).

[redacted]

11.2 Data review

Statistical analyses will be performed after a blind data review, for which the objectives are to ensure data integrity by detecting missing data and outlier values, identifying major protocol deviations, concomitant medications and adverse events reported during the clinical trial which could significantly bias the endpoints, and to define Full Analysis Set (FAS) and Per Protocol (PP) study populations. The three arms will be labelled as "A", "B" or "C" without information on the nature of each arm, in order to ensure blinding to participants and researchers. Thereby, the direction of any effect is not known while the outcome per arm can be taken into account to identify potential outliers, protocol deviations, etc.

Numbers will be recorded as decimals with a point registration. After closure of the data input, no changes in outcome can be made anymore. All relevant information, such as unity of measurement and reason of a missing value, should be available.

11.3 Software environment

The analyses are performed using SAS® software (version n° 9.4 or higher).

11.4 Significance level

The global alpha type I error with bilateral hypotheses for this study will be fixed to 5%.

For the first ranked endpoint, two superiority comparisons of the means of the SPID for each treatment arm will be performed. Considering that the two comparisons need to be stat[redacted]

Other statistical tests will be two-sided at the 5% level of significance.

11.5 Analysis populations

Full Analysis Set (FAS): according to the intention-to-treat (ITT) principle, all randomized participants treated with at least one dose of treatment and with at least one post-baseline assessment are included in the analysis in the arm to which they were initially randomized and all their data is used regardless of protocol deviations during the study

Per-protocol (PP): All subjects from the FAS for whom no major protocol violations/deviations occurred. The rules for the allocation of subjects to each of the analysis populations will be defined and documented during data review meetings held prior to database lock. During data review meetings, based on minor or major protocol deviations recorded, subjects may be excluded from the PP population.

Safety population: all randomized participants treated with at least one dose of treatment are included in the analysis in the arm they actually received.

11.6 Missing data handling

Missing data will not be replaced except for the ranked endpoint.

[redacted]

[redacted] be considered for the analysis of time points occurred after the intake of rescue medication.

11.7 Calculated variables

All variables will be mapped according to Clinical Data Interchange Standards Consortium (CDISC) format. Calculated variables will be described in the statistical analysis plan.

11.8 Descriptive statistics

The following descriptive statistics will be presented:

- For quantitative variables: number of analyzed values, number of missing values, mean, standard deviation, minimum, maximum, median and interquartile range. When relevant, confidence intervals will be calculated for the mean or median.
- For qualitative variables: number of analyzed values, number of missing values, number and percentage of observations in each category of variable. Except if otherwise specified, percentages will be calculated using the number of analyzed value as denominator. When relevant, confidence intervals of proportions will be calculated.

Descriptive analysis will be performed overall and by treatment group and stratification group.

11.9 Efficacy assessment

11.9.1 Efficacy population

The main analysis is conducted on the FAS population with a robustness analysis on PP population and according to missing data handling strategy described in section 11.6.

11.9.2 Efficacy analysis

The efficacy analysis is based on the following ranked efficacy endpoints:

1. Sum of Pain Intensity Differences at 6 hours ($SPID_{0-6h}$)
2. Total Pain Relief at 6 hours ($TOTPAR_{0-6h}$)
3. Number and proportion of responder participants at 6 hours
4. [redacted]

[redacted]

- If superiority is demonstrated for Total Pain Relief at 6 hours, the 3rd ranked efficacy endpoint on number and proportion of responder participants at 6 hours will be tested.
- If superiority is demonstrated for number and proportion of responder participants at 6 hours, the 4th ranked efficacy endpoint on PGIC questionnaire will be tested.
- If superiority is demonstrated for PGIC questionnaire, the 5th ranked efficacy endpoint on onset of pain relief will be tested.

The ranked efficacy endpoints will be defined and analysed as follow:

Sum of Pain Intensity Differences at 6 hours ($SPID_{0-6h}$) following the first IMP intake.

$SPID_{0-6h}$: time-weighted summary measure of the total area under the pain intensity difference curve that integrates serial assessments of pain during the first 6 hours after the first IMP intake.

[redacted]

A secondary analysis of the first ranked endpoint with a linear mixed model will be performed to provide the estimate of the least square (LS) means difference between the three groups in the SPID at 6 hours. This model will include the treatment as fixed factor, the baseline value of VAS and pain at

baseline group (stratification factor) as covariates. For comparison of combination difference in LS means of VAS, the two-sided 95% confidence interval (CI) of this difference and corresponding p-value (with 4 decimal places) will be computed. The superiority of the combination above each individual active substance will be demonstrated if whole two-sided confidence interval of the difference will be above zero.

Total Pain Relief at 6 hours ($TOTPAR_{0-6h}$) following the first IMP intake, measured with a 5-point verbal rating scale (none – a little – some – lot – complete pain relief).

TOTPAR: time-weighted summed measure of the total area under the pain relief curve that integrates serial assessments of pain during the first 6 hours after IMP intake.

[redacted]

[redacted]

Number and proportion of responder participants at 6 hours following the first IMP intake.

A responder participant is a subject who achieve a reduction of 50% of pain intensity compared to baseline.

The frequency, percentage and 95% CI of responder will be described according to treatment arms and group of pain at baseline.

Comparisons of responder participants between the 3 treatment arms will be made using the $\chi 2$ test, the corrected $\chi 2$ test or Fisher exact test, according to the expected values under the assumption of independence.

The patient's Global Impression of Change (PGIC) questionnaire assessed 6 hours after the first IMP intake or at time of the first intake of rescue medication (whichever happens first).

The PGIC questionnaire is a 7-point categorical scale (1= very much improved; 2= much improved; 3= minimally improved; 4= no change; 5= minimally worse; 6= much worse; 7= very much worse).

The frequency, percentage and 95% CI of each category will be described according to treatment arms and group of pain at baseline.

Comparisons of PGIC questionnaire between the 3 treatment arms will be made using the $\chi 2$ test, the corrected $\chi 2$ test or Fisher exact test, according to the expected values under the assumption of independence.

The onset of pain relief, defined as the time to reach a pain intensity score ≤ 30 mm on a 100-mm pain intensity VAS during the first 6 hours after the first IMP intake.

Score of Pain intensity will be assessed by the participant at defined time points (T30, T45, T60, T90, T120, T150, T180, T240, T300, T360 min). The time point of the first assessment obtaining a score ≤ 30 mm will be retained as time score of onset of pain relief.

The time to reach a pain intensity score ≤ 30 mm will be described in terms of probability of occurrence and confidence interval using the Kaplan-Meier method. The time of origin is the time of baseline and the time to event is the difference between the time to reach a pain intensity score ≤ 30 mm on a 100-mm VAS within the first 6 hours after IMP intake and the time of baseline in minutes. Participants using rescue medication will be censored at the time of intake of rescue medication. The different treatment groups are compared using the log-rank test.

11.9.3 Exploratory efficacy analysis

The following analysis of exploratory efficacy endpoints will be described overall, by treatment arm and group of pain at baseline depending on the nature of the variable on the FAS and PP population:

- Total Pain Relief at 1 hour ($TOTPAR_{0\text{-}1h}$), 2 hours ($TOTPAR_{0\text{-}2h}$), 3 hours ($TOTPAR_{0\text{-}3h}$), and 4 hours ($TOTPAR_{0\text{-}4h}$) following the first IMP intake, measured with a 5-point verbal rating scale (0 = none – 1 = a little – 2 = some – 3 = a lot – 4 = complete pain relief).
- Sum of Pain Intensity Differences at 1 hour ($SPID_{0\text{-}1h}$), 2 hours ($SPID_{0\text{-}2h}$), 3 hours ($SPID_{0\text{-}3h}$), and 4 hours ($SPID_{0\text{-}4h}$)
- The Pain Intensity Differences (PID) assessment at the following time-points: at T30, T45, T60, T90, T120, T150, T180, T240, T300 and T360 min post-dose from the pre-dose value.
- [redacted]

Comparisons between treatment arms will be performed depending on the nature of the variable:

- Comparisons of two or more qualitative variables are made using the $\chi 2$ test, the corrected $\chi 2$ test or Fisher exact test, according to the expected values under the assumption of independence.

- Comparisons of qualitative and quantitative variables are made using a Student test (parametric test comparing means) or Mann-Whitney-Wilcoxon test (nonparametric test comparing ranks) depending on the distribution of the variable of interest. Transformations to normalize the distribution of the variable can be performed if necessary.
- The risks of first occurrence of the outcome are described in terms of probability of occurrence and confidence interval using the Kaplan-Meier method. The time of origin is the time of baseline and the time to event is the difference between the time of diagnosis of the event and the time of baseline. The different treatment arms are compared using the log-rank test.

11.10 Safety analysis

The safety analysis will be performed on the safety population and described overall, by treatment arm and by group of pain at baseline using descriptive statistics.

Safety will be assessed during the study using reporting of adverse events (AEs). All AEs, Serious Adverse Event (SAE), non-serious AEs-related to IMP, or AE leading to dose modification, interruption and discontinuation of IMP will be described.

The frequencies and percentages of adverse events (AEs) and serious adverse events (SAEs) will be described.

The frequencies and percentages of patients with at least one AE and SAE will be described.

The event will be described according to System Organ Class (SOC) and Preferred Term (PT) dictionary MedDRA coding and also intensity and severity.

No statistical comparison between treatment arms will be performed.

11.11 Treatment Compliance

The following compliance criteria will be described:

- Interval of intake in the ranges allowed by the protocol
- 2 capsules administered at each intake.

11.12 Interim analysis

No interim analysis is planned

11.13 Statistical analysis plan and changes to the statistical section of the study protocol

Any changes made to the statistical methodology presented in the study protocol will be reported in the Statistical Analysis Plan (SAP) and in the clinical study report.

Any changes to the initial statistical plan after the data review will result in an amendment to the SAP. The last validated version of the statistical analysis plan before unblinding shall be considered as the final version of this document.

12 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

12.1 Source documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, patients' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

12.2 Case Report Forms

Electronic Case report forms (eCRF) must be completed for each subject screened/enrolled in this

The investigator will document patient data in his/her own patient files. These patient files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation of the centres.

13 ETHICAL CONSIDERATIONS

13.1 Regulatory statement

The study will be conducted in compliance with Good Clinical Practice guidelines (R2), the most recent revised version of the Declaration of Helsinki *(Fortaleza, October 2013, copy attached in Appendix 6)* and the European Directive 2001/20/EC on 4th April 2001 *(on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use)*.

The protocol and subsequent substantial amendments *(if applicable)* are to be submitted to the local and or central Ethics Committee and national Competent Authority (CA) for approvals in each participating country.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to p[redacted]

The enrolment of patients in the study could be started in a given participating country only after written approvals of the corresponding national Ethics Committee and Competent Authority.

13.2 Data Safety monitoring board

No Data Safety Monitoring Board (DSMB) will be set-up for this study for the following reasons:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

13.3 Financial disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

13.4 Informed consent process

The investigator will explain the nature of the study to the participant and answer all questions regarding the study. The Investigator provides each patient with relevant, comprehensive, verbal and written information regarding the objectives and procedures of the study, as well as the possible risks involved. A patient information sheet will be given to the patient.

The patient should have enough time and opportunity to inquire about study details. All his/her questions should be answered in a satisfactory manner. The patient must be informed about his/her right to withdraw from the study at any time.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

Signed informed consent must be obtained from the patient prior to undertaking any study-related procedure and before any VAS is performed during screening.

[redacted]

[redacted] language will be submitted to the Ethics Committees for approvals, together with the protocol.

[redacted]

[redacted] the study is being conducted and must not improperly influence the patient's decision to participate.

13.6 Data protection

Patients will be assigned to a unique identifier by the Sponsor (2 digit-number for site identification + 2 digit-number for patient identification). Any participant records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

13.7 Dissemination of clinical data

UNITHER Pharmaceuticals commits to disclose information from the protocol and clinical study results information on clinical trial registries: Clinicaltrials.gov.

The clinical study registration will be completed before first patient enrolled, and the clinical study results summary will be reported within one year after primary outcome completion and/or study completion date.

13.8 Data quality assurance

All patient data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

[redacted]

13.9 Source documents

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time in each centre. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X rays, patient files, and records kept at pharmacies, laboratories, and medico technical departments involved in a clinical trial.

[redacted]

Also, current medical records must be available to facilitate source data verification and review, and the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

13.10 Audit and on-site inspections

Prior to the start of the study, the investigator is required to confirm his/her agreement to conduct the study in accordance with the protocol and to give access to all relevant data and records to UNITHER Pharmaceuticals monitors, auditors, and designated agents of UNITHER Pharmaceuticals, IRBs/IECs, and regulatory authorities as required.

If an inspection of the site is requested by a regulatory authority, the investigator must inform UNITHER Pharmaceuticals and designated agents of UNITHER Pharmaceuticals (EXCELYA BORDEAUX) immediately that this request has been made.

13.11 Insurance

The Sponsor certifies subtracting a contract of public liability insurance to provide patients with compensation for any injury, including the consequences of administration of the investigational product and of the study procedures.

In case of injury or disability resulting from participation in the study, the patient is requested to promptly inform the Investigator responsible for the study.

The Insurance certificates are to be provided to the local Ethics Committee and national Competent Authority in each participating country at the submission for clinical trial approvals.

13.12 Publication policy

The results of this study are UNITHER Pharmaceuticals proprietary and cannot be published or presented in any scientific meeting without any agreement from the sponsor. If UNITHER Pharmaceuticals agree that the data may be published or presented at scientific meetings, the designated investigator agrees to submit all manuscripts or abstracts to the Sponsor before any submission. This allows the Sponsor to protect proprietary information and to provide comments.

[redacted]

[redacted].

14 COMPLETION OF THE STUDY

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and UNITHER Pharmaceuticals or EXCELYA Bordeaux. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and UNITHER Pharmaceuticals or EXCELYA Bordeaux. The investigator will provide a final report to the IEC/IRB following conclusion of the study and will forward a copy of this report to UNITHER Pharmaceuticals or EXCELYA Bordeaux or their representative.

[redacted]

[redacted] review and sign the final study report in accordance with the European Medicines Agency (EMA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit.

15 COVID-19

This clinical trial is designed in a context where the COVID-19 (coronavirus disease 2019) pandemic is still active worldwide. The impact of the COVID-19 pandemic on this trial, on the recruitment and the continued involvement of participants, has been assessed and will be regularly reassessed according to the international and local situations.

The Sponsor undertakes to scrupulously follow the latest version of Guidance on the management of clinical trials during the COVID-19 pandemic issued by EMA and to comply with the national recommendations of each participating countries.

Actions will be proportionate and based on benefit-risk considerations, on contingency provisions taken nationally and locally by the authorities, with priority given to the impact on the health and safety of the trial participant.

Measures would be agreed with investigators and could be:

- Postponement or complete cancellation of patient visits to ensure that only strictly necessary visits are performed at sites;
- A temporary halt of the trial at some or all trial sites;
- Interruption or slowing down of recruitment of new trial participants
- Extension of the duration of the trial;
- Postponement of trial or of activation of sites that have not yet been initiated;
- Monitoring of IMP management (expiry date)

The risk assessment and measure will be filed in eTMF.

16 LIST OF REFERENCES

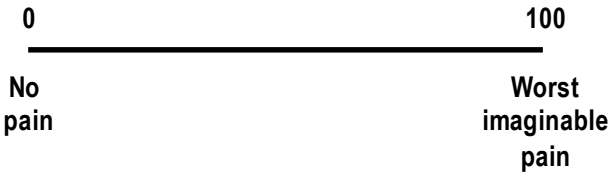
1. [redacted]

17 APPENDICES

17.1 [redacted]

[redacted]

Using a ruler, the score is determined by measuring the distance (mm) on the 100 mm line between the “no pain” anchor and the patient's mark, providing a range of scores from 0–100.



17.2 Appendix 2 - Pain relief – 5-point Verbal Rating Scale (VRS)

Patients use a 5-point verbal rating scale for the subjective assessment of post-operative pain relief.

[redacted]

☐ **0** = No relief of pain ☐ **1** = Little relief ☐ **2** = Some relief ☐ **3** = A lot of relief ☐ **4** = Complete relief of pain

17.3 Appendix 3 -Patient Global Impression of Change (PGIC) Scale

The Patient Global Impression of Change (PGIC) is the PRO counterpart to the Clinical Global Impressions scale (CGI). It consists of one item taken from the CGI and adapted to the patient. This scale evaluates all aspects of patients' health and assesses if there has been an improvement or decline in clinical status.

17.4 Appendix 4 - Names and Details of Contract Research Organisation (CRO)

Unither-Pharmaceuticals has contracted EXCELYA Bordeaux, an international CRO:

17.5 Appendix 5 – SAE Form

Serious Adverse Event Report Form

Sponsor: **Protocol n°:**

Site N°: **Investigator:**

Patient N°

[redacted]

Serious Adverse Event Report Form

Sponsor: **Protocol n°:**

Site N°: **Investigator:**

Patient N°

This SAE report is : ☐ Initial report

[redacted]

Serious Adverse Event Report Form

Sponsor: **Protocol n°:**

Site N°: **Investigator:**

[redacted]

Serious Adverse Event Report Form

Sponsor: **Protocol n°:**

Site N°: **Investigator:**

Patient N°

[redacted]

Serious Adverse Event Report Form

Sponsor: **Protocol n°:**
Site N°: **Investigator:**
Patient N°

[redacted]

Serious Adverse Event Report Form

Sponsor: **Protocol n°:**
Date of last visit: **Visit Date:**
Investigator: **Site N°**

Comments:

Completed by:			
Name	Position	Signature	Date
Investigator's signature			
Name		Signature	Date

17.6 Appendix 6 – Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The

responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, Sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the Sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, Sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, Sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

PROTOCOL AGREEMENT