STUDY TITLE:	Maxigesic® IV Bunionectomy Study: A Phase 3, Randomized, Double-Blind, Multiple-Dose, Parallel-Group and Placebo-Controlled Study of IV Maxigesic®, IV acetaminophen and IV ibuprofen for the Treatment of Acute Postoperative Pain After Bunionectomy
PROTOCOL NUMBER:	AFT-MXIV-07
TRIAL REGISTRATION NUMBER:	NCT02689063
IND APPLICATION No.	124213
STUDY DRUG:	Maxigesic® IV
DEVELOPMENT PHASE:	Phase III
INDICATION:	Analgesia for acute postoperative pain.
SPONSOR:	AFT Pharmaceuticals Ltd Level 1, 129 Hurstmere Rd, Takapuna, Auckland, NEW ZEALAND
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AMENDMENT 03 DATE:	January 4th, 2017

CONFIDENTIAL – PROPRIETARY INFORMATION

INTERNAL APPROVAL FORM

CLINICAL RESEARCH PROTOCOL

STUDY DRUG	Maxigesic® IV: Intravenous acetaminophen 1000 mg + intravenous ibuprofen 300 mg/100 ml solution for infusion
PROTOCOL TITLE	Maxigesic® IV Bunionectomy Study: A Phase 3, Randomized, Double-Blind, Multiple-Dose, Parallel-Group and Placebo-Controlled Study of IV Maxigesic®, IV acetaminophen and IV ibuprofen for the Treatment of Acute Postoperative Pain After Bunionectomy
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PROTOCOL SYNOPSIS

Name of Sponsor	AFT Pharmaceuticals Ltd
Name of Active Ingredient	Acetaminophen and Ibuprofen
Title of Study	A Phase 3, Randomized, Double-Blind, Multiple-Dose, Parallel-Group and Placebo-Controlled Study of IV Maxigesic®, IV Acetaminophen and IV Ibuprofen for the Treatment of Acute Postoperative Pain After Bunionectomy
Study Centre	Optimal Research LLC 3200 Red River, Suite 301. Austin, Texas 78705 Dr. Stephen Daniels, DO-Principal Investigator
Phase of Development	Phase III
Background and Rationale	The combination of acetaminophen and ibuprofen in a single tablet (Maxigesic®: acetaminophen 500 mg + ibuprofen 150 mg) has been shown to be effective in the treatment of postoperative pain (third molar extraction) and superior to the same dose of either acetaminophen or ibuprofen alone (Merry AF. et al, 2010). A similar oral combination (acetaminophen 325 mg + ibuprofen 97.5 mg given as up to three tablets [acetaminophen 975mg + ibuprofen 292.5mg] per dose), developed for registration and use in the USA was evaluated in a large Phase 3 clinical studies in 408 subjects undergoing dental surgery (IND No. 107,435 [NCT01420653]. The combination was statistically superior to both acetaminophen and ibuprofen monotherapy and placebo, as measured by the primary and secondary endpoints. AFT Pharmaceuticals Ltd. has been developing a fixed-dose combination of acetaminophen 1000 mg and ibuprofen 300 mg/100 ml solution for infusion (Maxigesic® IV) for the temporary relief of postoperative pain, when administration by intravenous route is clinically justified by an urgent need to treat pain or hyperthermia and/or when other routes of administration are not possible. A Phase III efficacy study (AFT-MXIV-02) is proposed to determine the analgesic effects of the fixed dose combination product Maxigesic® IV versus its individual components (acetaminophen IV and ibuprofen IV) and placebo in participants with acute post-operative pain after bunionectomy.
Objectives	**Efficacy Primary Objective:** To determine the efficacy of Maxigesic® IV, acetaminophen IV, ibuprofen IV versus placebo IV for the treatment of acute postoperative pain after bunionectomy as measured by the summed pain intensity difference (SPID) (calculated as a time-weighted average) over 0 to 48 hours (SPID-48) after Time 0. **Safety Objectives:** To determine the incidence of treatment-emergent adverse events (AEs) and changes in vital sign measurements.
Study Design	This is a phase 3, multicentre, randomized, double-blind, multiple-dose parallel-group, placebo-controlled study to evaluate the safety and efficacy of Maxigesic® IV (acetaminophen 1000mg/100ml + ibuprofen

	300mg/100ml solution for infusion) 4 times daily, IV acetaminophen (1000mg/100ml solution for infusion) 4 times daily, IV ibuprofen (300mg/100ml solution for infusion) 4 times q6h and placebo (IV saline 100ml solution) in subjects with acute postoperative pain after bunionectomy.
Number of Participants	275 participants (75 in each active group and 50 in placebo)
Main Inclusion Criteria	Main Inclusion Criteria: ➢ Male or female ≥ 18 and ≤ 65 years of age. ➢ Classified as P1 to P2 in the American Society of Anesthesiologists (ASA) Physical Status Classification System. ➢ Has undergone distal, primary, unilateral, first metatarsal bunionectomy (with osteotomy and internal fixation) with no additional collateral bony procedures. ➢ Experiences a pain intensity rating of ≥ 40 mm on a 100-mm Visual Analogue Scale (VAS) during the 9-hour qualification period after discontinuation of the anesthetic block.
Study Drugs & Treatment	Each participant will be randomly allocated to receive one of the following study treatments: Treatment A: Maxigesic® IV (intravenous acetaminophen1000 mg + intravenous ibuprofen 300 mg/100 ml solution for infusion) Treatment B: Intravenous acetaminophen 1000 mg/100mL solution for infusion Treatment C: Intravenous ibuprofen 300 mg/ 100mL solution for infusion Treatment D: Placebo (intravenous saline, 100 mL solution for infusion)
Study Drug Administration	All study drugs will be administered by injection into a dedicated indwelling venous cannula, infused over 15 minutes. The study drugs will be administered, every 6 hours (q6h) for 48 hours (a total of 8 doses).
Duration of Treatment	The estimated duration of the study for each subject is approximately 40 days, which includes a screening period up to 28 days, a 3-day treatment period (approximately 72 hours of confinement with 48 hours of treatment), and a post treatment follow-up phone call within 5 to 9 days after surgery.
Rescue Analgesia	As a primary rescue analgesia oxycodone 5 or 10 mg will be allowed orally every 4-6 hours as needed for pain before the anaesthetic infusion is discontinued, and as rescue medication after the anaesthetic infusion is discontinued. If adequate pain relief is not achieved with oxycodone, as a secondary rescue analgesia, 2-4 mg intravenous morphine sulphate will be allowed to be administered every 4 hours, as needed.
Evaluation of Efficacy	**Primary Endpoint**: The primary endpoint is the VAS summed pain intensity difference (VAS SPID) (calculated as a time-weighted average) over 0 to 48 hours (VAS SPID-48) after Time 0. Secondary Endpoints: ➢ VAS Pain intensity difference (PID) at each scheduled assessment

	time point after Time 0 ➢ VAS Pain intensity score at each scheduled assessment time point ➢ VAS SPID over 0 to 6 hours (SPID-6), over 0 to 12 hours (SPID-12), and over 0 to 24 hours (SPID-24) after Time 0 ➢ Summed pain relief (TOTPAR) (calculated as a time-weighted average) over 0 to 6 hours (TOTPAR-6), over 0 to 12 hours (TOTPAR-12), over 0 to 24 hours (TOTPAR-24) after Time 0, and over 0 to 48 hours (TOTPAR-48) after Time 0 ➢ Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief) using the two-stopwatch method ➢ Pain relief score on a 5-point categorical scale at each scheduled time point after Time 0 ➢ Peak pain relief ➢ Time to peak pain relief ➢ Time to first perceptible pain relief ➢ Time to meaningful pain relief ➢ Proportion of subjects using rescue medication ➢ Time to first use of rescue medication (duration of analgesia) ➢ Total use of rescue analgesia over 0 to 24 hours and over 0 to 48 hours ➢ Patient's global evaluation of study drug
Evaluation of Safety	The safety endpoints are the incidence of treatment-emergent adverse events (AEs) and changes in vital sign measurements.
Sample Size Calculation	In total, 275 participants (75 in each active group and 50 in placebo) will be randomised into the study. This sample size will provide 80% power to detect as statistically significant (2-sided α=0.05) any difference >10.5mm [ES=0.6] in mean time-adjusted SPID between Maxigesic® IV and each of the three comparator study groups.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AB	Anesthetic Block
ADL	Activity of Daily Living
AE(s)	Adverse event(s)
ANOVA	Analysis of Variance
AUC	Area under the curve
BOCF	Baseline Observation Carry Forward
CRF(s)	Case Report Form(s)
CFR	Code of Federal Regulation
DSMB	Data Safety Management Board
EC	Ethics Committee
EP	Evaluable Portion
EU	European Union
GCP	Good Clinical Practice
GI	Gastrointestinal
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ITT	Intention to Treat
IV	Intravenous
LOCF	Last Observation Carry Forward
Maxigesic® IV	Intravenous acetaminophen 1000mg + intravenous ibuprofen 300mg/100 ml solution for infusion
NSAID	Non-steroidal Anti-Inflammatory Drug
PACU	Post-anaesthetic Care Unit
PP	Per-protocol
PSB	Popliteal Sciatic nerve Block
SAE(s)	Serious Adverse Event(s)
SAER	Serious Adverse Event Report
SPID	Summed Pain Intensity Difference
TOTPAR	Total Pain Relief
VAS	Visual Analogue Scale
WHO	World Health Organisation

1. INTRODUCTION

This protocol describes a Phase III study designed to examine the analgesic efficacy and safety of a combination of intravenous acetaminophen and ibuprofen (Maxigesic® IV). Confirmatory clinical trials are necessary to prove analgesic efficacy, preferably using parallel group comparisons in which the fixed combination is compared to its individual substances in a factorial design, and preferably including a placebo arm (1).

The analgesic efficacy of the combination acetaminophen and ibuprofen has been widely reported and the fixed combination Maxigesic® tablets (as two tablets, total dose acetaminophen 1000mg + ibuprofen 300mg) have been shown to have superior analgesic efficacy than either acetaminophen or ibuprofen alone in acute postoperative pain from third molar removal (2) .

In another recently completed phase 3 study, Maxigesic® 325 tablets (acetaminophen 325mg + ibuprofen 97.5mg per tablet, administered as 3 tablets per dose) has clearly demonstrated superior analgesic efficacy than either acetaminophen 325 mg alone or ibuprofen 97.5mg alone in acute postoperative pain from third molar removal (AFT-MX-6) (3).

However, the use of oral analgesics in the immediate postoperative period may not be possible. Maxigesic® IV has been developed to allow a combination analgesic therapy with the administration of a single formulation in patients who are unable to take oral analgesics.

In a previous Maxigesic® IV single-dose, open label, 5 period crossover sequence PK study in 30 healthy volunteers, it was found that pharmacokinetic parameters for ibuprofen and paracetamol were very similar for the combination and monotherapy intravenous preparations; ratios of C_{max}, AUC_t, and $AUC_{0-\infty}$ values fell within the 80-125% acceptable bioequivalence range. Precise dose proportionality for both compounds was also determined for the half dose of the intravenous formulation compared with the full dose. The relative bioavailability of paracetamol (93.78%) and ibuprofen (96.45%) confirmed the pharmacokinetic equivalence between the oral and intravenous formulations of the fixed dose combination (4).

Clinical safety assessment for all subjects was carried out to evaluate their tolerability to the study medications. Study subjects demonstrated good tolerance to the study's treatments.

Following this, a phase 3 study has been planned to investigate the clinical efficacy and safety of Maxigesic® IV in a post-operative pain model.

This study will be conducted in compliance with Good Clinical Practices (GCP) including the Declaration of Helsinki and all applicable regulatory requirements.

1.1. Background

Effective treatment of postoperative pain is essential to patient outcome and well-being (5). Clinically, inadequate pain relief can have profound implications including cardiovascular, respiratory and gastrointestinal (GI) adverse effects, emotional and physical suffering, sleep

disturbances, delayed mobilisation (which can promote thromboembolism and delayed rehabilitation) and progression to chronic pain syndromes. Economically, undertreated pain can lead to extended hospital stays and/or readmission (6–8).

Opioids are the gold standard for the treatment of postoperative pain but their use is often limited by dose dependent adverse events such as nausea and vomiting, constipation, sedation and respiratory depression (7). Sustained opioid use can also lead to tolerance, resulting in increased dosing requirements, dependence and a subsequent increase in adverse events.

The World Health Organisation (WHO) advocates the use of multimodal analgesia for optimal pain control. Multimodal, or balanced, analgesia acts at different sites within the central and peripheral nervous systems to synergistically improve pain control while reducing opioid related adverse events (9,10). The first step on the WHO pain relief ladder involves the use of non-opioid analgesics, such as acetaminophen and NSAIDs (9). Both acetaminophen and ibuprofen are effective analgesics that have been used for many years. Both are available without a prescription and have well-established safety records (6).

The use of oral analgesics in the postoperative period may not be suitable due to patient intubation, sedation, postoperative nausea and vomiting and reduced gastric motility. Oral medications often have a delayed clinical effect due to inconsistent absorption in hospitalised patients (11).

A fixed combination of acetaminophen and ibuprofen intravenous formulation may improve patient analgesia in the postoperative period, whilst simplifying dosing.

1.2. Study Drug Rationale

While there are many analgesic options open to physicians most have limitations. For example, fixed dose combinations that include opioids carry the risks of the side effects and dependency associated with opioid drugs. Acetaminophen and ibuprofen are well established analgesics with excellent safety records in both adults and children.

AFT Pharmaceuticals Ltd. has been developed a fixed-dose combination of acetaminophen 1000 mg and ibuprofen 300 mg/100 ml solution for infusion (Maxigesic® IV) for the temporary relief of postoperative pain, when administration by intravenous route. This is clinically justified by an urgent need to treat pain or hyperthermia when other routes of administration are not possible or prudent.

1.3. Study Rationale

1.3.1. *Rationale: Study Medication*

Acetaminophen and ibuprofen are well established analgesics with excellent safety records in both adults and children. Maxigesic® tablets have been previously shown to be effective in the relief of postoperative pain but their usefulness in the postoperative period may be limited due to medical interventions and patient factors previously described. An

intravenous formulation will allow administration to patients who are in urgent need to treat pain or hyperthermia when other routes of administration are not possible or prudent.

1.3.2. *Rationale: Comparator*

This trial design follows the EMA/CHMP/970057/2011 Guideline on the clinical development of medicinal products intended for the treatment of pain (12). This guideline mandates that confirmatory clinical trials are necessary to prove efficacy, preferably by parallel comparisons in which the fixed combination is compared to its individual substances and should include a placebo group when feasible. Maxigesic® IV will therefore be compared to intravenous acetaminophen alone, intravenous ibuprofen alone and placebo.

1.3.3. *Rationale: Treatment Period*

To minimize the potential for carryover effects from operative anesthesia medications and to allow a uniform administration and evaluation of the study medications, the investigational drugs will be administered on the morning of the day after surgery.

1.4. Known and Potential Risks and Benefits

All drugs and all clinical studies have risks. However, these are likely to be minimal in the present study because both acetaminophen and ibuprofen have been used extensively for many years at these dose levels. The dose ranges in this study fall well within the range that has been used worldwide for over 15 years.

The potential benefit of this study lies in its potential to improve the quality of analgesia for participants requiring acute pain relief following surgery, and improved safety of combination analgesia for this purpose: reducing the amount of ibuprofen offers the potential to reduce the rate of known NSAID adverse events while improving efficacy due to the addition of acetaminophen. Recently completed preclinical studies Maxigesic® IV was considered to have little potential to produce local irritation when administered intravenously at the recommended dose level

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1. Study Hypothesis

The study hypothesis is that the analgesic effect of Maxigesic® IV (intravenous acetaminophen 1000 mg + intravenous ibuprofen 300 mg/ 100 ml solution for infusion) is greater than that of intravenous acetaminophen 1000 mg/100 ml solution for infusion given individually or placebo.

2.2. Objectives and Endpoints

2.2.1. *Efficacy Objectives*

2.2.1.1. Primary Objective/Endpoint

To determine the efficacy of Maxigesic® IV, acetaminophen IV, ibuprofen IV versus placebo IV for the treatment of acute postoperative pain after bunionectomy as measured by summed pain intensity difference (SPID) (calculated as a time-weighted average) over 0 to 48 hours (SPID-48) after time 0.

2.2.1.2. Secondary Objectives/Endpoints

- Pain intensity difference (PID) at each scheduled assessment time point after Time 0
- Pain intensity score at each scheduled time point
- SPID over 0 to 6 hours (SPID-6), over 0 to 12 hours (SPID-12), and over 0 to 24 hours (SPID-24)
- Summed pain relief (TOTPAR) (calculated as a time-weighted average) over 0 to 6 hours (TOTPAR-6), over 0 to 12 hours (TOTPAR-12), over 0 to 24 hours (TOTPAR-24) and over 0 to 48 hours (TOTPAR-48)
- Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief) using the two-stopwatch method)
- Pain relief score on a 5-point categorical scale at each scheduled time point after Time 0
- Peak pain relief
- Time to peak pain relief
- Time to first perceptible pain relief
- Time to meaningful pain relief
- Proportion of subjects using rescue medication
- Time to first use of rescue medication (duration of analgesia)
- Total use of rescue analgesia over 0 to 24 hours and over 0 to 48 hours
- Patient's global evaluation of study drug

2.2.1.3. Safety Objectives

The safety endpoints are the incidence of treatment –emergent adverse events (AEs) and changes in vital sign measurements.

3. STUDY DESIGN

3.1. Basic Study Design Characteristics

This study is a Phase III, placebo-controlled, randomised, double-blind, parallel-design trial to investigate the analgesic efficacy of Maxigesic® IV compared with the individual components alone and placebo. A flow chart providing a schematic representation of the study design can be found in Section 3.2.

Eligible subjects will complete all screening procedures within 28 days before the surgery. At Screening, subjects will provide written informed consent to participate in the study

before any protocol-specified procedures or assessments are completed.

Subjects will be admitted to the study site on the morning of the scheduled surgery (Day 0), will remain at the study site until postoperative Day 3 (a total of 3 nights at the study site), and will be followed up with a phone call which occurs 5 to 9 days after surgery.

On Day 0, subjects who continue to meet all study entry criteria will undergo standard distal first metatarsal bunionectomy procedure using a standardized regimen of regional anesthesia. The regional anesthetic technique to be used for this surgery comprises a combination of a PSB to establish and maintain surgical field anesthesia (local anesthesia using a Mayo block with a short acting anesthetic will be allowed to augment surgical field anesthesia at the surgeons discretion) and a continuous sciatic infusion to provide an effective method of controlling pain in the immediate postoperative period.

The PSB will be administered using modifications of the Singelyn technique (13). Subjects will receive midazolam and/or propofol for initial sedation at the anesthesiologist's discretion. After adequate sedation is achieved, the anesthesiologist will inject approximately 5 mL lidocaine 1% (plain) (or suitable short acting local anesthetic without epinephrine) locally to anesthetize the skin, and will determine the location of the sciatic nerve for the PSB using a nerve stimulator per standard technique. Once the appropriate location is determined, the anesthesiologist will inject 40 mL of ropivacaine 0.5% to establish the PSB. Subsequently a catheter will be placed in the proximity of the popliteal sciatic nerve for delivery of postoperative anesthesia. If the PSB is not sufficient to provide adequate surgical anesthesia, a standard Mayo block (local anesthesia) may be established using lidocaine 2% (plain) not to exceed 25 mL. The time, date, dose, and route of all local anesthetics will be recorded in the CRF.

The regional anesthesia will be established using a popliteal sciatic nerve block (PSB) after which subjects will undergo primary, unilateral, first metatarsal bunionectomy under regional anesthesia. The regional anesthesia will be continued postoperatively via a continuous anesthetic infusion.

Subjects may receive supplemental analgesia with an opioid product (oxycodone 5 or 10 mg every 4-6 hours as needed) after surgery and before randomization to help control breakthrough pain if the regional anesthetic infusion fails to provide adequate anesthesia.
Though sites will be encouraged to use only the oxycodone as supplemental analgesia if adequate pain relief is not achieved with oral oxycodone, as a secondary rescue analgesia, 2-4 mg intravenous morphine sulphate will be allowed to be administered every 4 hours, as needed. If the regional anesthetic infusion and supplemental primary and secondary analgesia do not effectively control the subject's postoperative pain, then the subject will be discontinued from the study and pain will be managed per standard of care/investigator discretion.

On Day 1, the regional anesthetic infusion will be discontinued at approximately 3 AM. When subjects request pain medication, they will be asked to rate their pain intensity using the 100 mm VAS scale assessment (0-100) (Appendix 3).

During the 9-hour qualification period after discontinuation of the anesthetic block, subjects who experience a pain intensity rating of ≥ 40 mm on the VAS are eligible to be enrolled into the study. If their pain intensity ratings do not meet the minimum entry criteria within 9 hours of discontinuation of the regional anesthesia, subjects will not be eligible for enrollment and will receive routine standard postoperative care at the investigator's discretion.

Once the pain intensity entry criteria are met, subjects will be randomly assigned to one of four treatment groups mentioned in section 5.1.1.

A detailed investigational plan can be found in Section 7.1 and Table 1.

3.2. Schematic study diagram

Visit 1			Visit 2				Visit 3
Consent	**Screening** (within 28 days prior to randomization)	**Day 0 Surgery**	**Day 1 Post-surgery Qualification** (within 9 hours discontinuation from the anesthetic block)	**Randomisation to study drug**	**Post-Surgery** (D1 and D2)	**Discharge** (D3)	**Follow-up Phone Call** (D5 to 9 after surgery)
Participants provided with information about the study	After consent, eligibility is checked.	Standard distal first metatarsal bunionectomy procedure using a standardized regimen of regional anesthesia.	Participants must be experiencing moderate to severe pain (≥ 40 mm on VAS) post-operatively to be randomized	Maxigesic® IV Acetaminophen IV Ibuprofen IV Placebo IV	Study drugs administered 4 times daily (total of 8 doses in 48 hours)	Participant diaries completed and safety assessment	Follow up safety data

3.3. Randomisation

Randomisation will occur at the study site once participant eligibility for the study is confirmed postoperatively. Eligibility will be confirmed on the first postoperative morning (Day 1) within the 9-hour qualification period after discontinuation of anesthetic block.

Each eligible participant will be assigned a unique study identification number and randomly assigned to treatment according to the computer generated randomization schedule.

The randomisation sequence will be computer-generated by the study statistician, in permuted blocks prior to any enrolment. The statistician will maintain a confidential schedule of participant numbers and drug allocation. The site will receive a set of individual sealed randomisation envelopes for each stratum; the envelope for a specific participant can be opened only if there is a medical emergency where medical management of the participant requires knowing the identity of the study drug the subject was administered.

3.4. Blinding

Blinding will be achieved by the use of matching vials prepared by the technical department of the sponsor who is not involved in the data collection.

Each vial of study drug will be labelled with the participant's study identification number.

The participant, investigator and study staff will be blinded to the assigned treatment until all participants have completed the protocol (including the follow-up) and after the study database has been locked. The participant's treatment group will be revealed only if there is a medical emergency where medical management of the participant requires knowing the identity of the study drug the subject was administered.

4. STUDY POPULATION

4.1. Number of Participants

In total, 275 subjects (75 subjects in each active and 50 subjects in placebo) who meet all the eligibility criteria will be enrolled and randomised into the study.

4.2. Inclusion Criteria

All subjects will be eligible for entry into the study if all of the inclusion criteria are met:

1. Is male or female ≥ 18 and ≤ 65 years of age.

2. Is classified by the anesthesiologist as P1 to P2 in the American Society of Anesthesiologists (ASA) Physical Status Classification System.

3. Has undergone primary, unilateral, distal, first metatarsal bunionectomy (osteotomy and internal fixation) with no additional collateral procedures.

4. Experiences a pain intensity rating of ≥ 40 mm on a 100-mm Visual Analogue Scale (VAS) during the 9-hour period after discontinuation of the anesthetic block.

5. Has a body weight ≥ 45 kg and a body mass index (BMI) ≤ 40 kg/m^2.

6. Female has negative pregnancy test results at screening (urine) and on the day of surgery prior to surgery (urine)..

7. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or practicing 1 of the following medically acceptable methods of birth control:

   - Hormonal methods such as oral, implantable, injectable, or transdermal contraceptives for a minimum of 1 full cycle (based on the subject's usual menstrual cycle period) before study drug administration.
   - Total abstinence from sexual intercourse since the last menses before study drug administration through completion of final study visit.
   - Intrauterine device (IUD).
   - Double-barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jellies or cream).

8. Is able to provide written informed consent to participate in the study and able to understand the procedures and study requirements.

9. Must voluntarily sign and date an informed consent form (ICF) that is approved by an Institutional Review Board (IRB) before the conduct of any study procedure.

10. Is willing and able to comply with study requirements (including diet, alcohol, and smoking restrictions), complete the pain evaluations, remain at the study site for approximately 72 hours, and will be followed up with a phone call at 7 ± 2 days after surgery.

4.3. Exclusion Criteria

A subject will not be eligible for study entry if any of the following exclusion criteria are met:

1. Has a known history of allergic reaction or clinically significant intolerance to acetaminophen, aspirin, opioids, or any nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen); history of NSAID-induced bronchospasm (subjects with the triad of asthma, nasal polyps, and chronic rhinitis are at greater risk for bronchospasm and should be considered carefully); or hypersensitivity, allergy, or significant reaction to sulfa (including sulfonamide) medicines, ingredients of the study drug, or any other drugs used

in the study including anesthetics and antibiotics that may be required on the day of surgery.

2. Has experienced any surgical complications or other issues that, in the opinion of the investigator, could compromise the safety of the subject if he or she continues into randomized treatment period or could confound the results of the study.

3. Has known or suspected history of alcoholism or drug abuse or misuse within 2 years of screening or evidence of tolerance or physical dependence before dosing with study drug.

4. Has any clinically significant unstable cardiac, respiratory, neurological, immunological, hematological, or renal disease or any other condition that, in the opinion of the investigator, could compromise the subject's welfare, ability to communicate with the study staff, or otherwise contraindicate study participation.

5. Has any ongoing condition, other than a condition associated with the current primary, unilateral, first metatarsal bunionectomy that could generate levels of pain sufficient to confound the results of the study (eg, gout, severe osteoarthritis of the target joint or extremity).

6. Has a history or current diagnosis of a significant psychiatric disorder that, in the opinion of the investigator, would affect the subject's ability to comply with the study requirements.

7. Has tested positive either on the urine drug screen or on the alcohol breathalyzer test. Subjects who test positive at Screening only and can produce a prescription for the medication from their physician may be considered for study enrolment at the discretion of the investigator.

8. Has a history of a clinically significant (investigator opinion) gastrointestinal (GI) event within 6 months before Screening or has any history of peptic or gastric ulcers or GI bleeding.

9. Has a surgical or medical condition of the GI or renal system that might significantly alter the absorption, distribution, or excretion of any drug substance.

10. Is considered by the investigator, for any reason (including, but not limited to, the risks described as precautions, warnings, and contraindications in the current version of the Investigator's Brochure [IB] for IV Maxigesic®), to be an unsuitable candidate to receive the study drug.

11. Is receiving systemic chemotherapy, has an active malignancy of any type, or has been diagnosed with cancer within 5 years before Screening (excluding treated squamous or basal cell carcinoma of the skin).

12. Is currently receiving anticoagulants (eg, heparin or warfarin).

13. Has received a course of systemic corticosteroids (either oral or parenteral) within 3 months before Screening (inhaled nasal steroids and regional/limited area application of topical corticosteroids (investigator discretion) are allowed).

14. Has received or will require any analgesic medication within 5 half-lives (or, if half-life is unknown, within 48 hours) before surgery.

15. Has a history of chronic use (defined as daily use for > 2 weeks) of NSAIDs, opiates, or glucocorticoids (except inhaled nasal steroids and regional/limited topical corticosteroids), for any condition within 6 months before study drug administration. Aspirin at a daily dose of ≤ 325 mg is allowed for cardiovascular prophylaxis if the subject has been on a stable dose regimen for ≥ 30 days before Screening and has not experienced any relevant medical problem.

16. Has been treated with agents that could affect the analgesic response (such as central alpha agents [clonidine and tizanidine], neuroleptic agents, and other antipsychotic agents) within 2 weeks before dosing with study drug.

17. Has a significant renal or hepatic disease, as indicated by clinical laboratory assessment (results ≥ 3 times the upper limit of normal [ULN] for any liver function test, including aspartate aminotransferase [AST], alanine aminotransferase [ALT], or creatinine ≥ 1.5 times the ULN).

18. Has any clinically significant laboratory finding at Screening that, in the opinion of the investigator, contraindicates study participation.

19. Has significant difficulties swallowing capsules or is unable to tolerate oral medication.

20. Previously participated in another clinical study of Maxigesic® IV or received any investigational drug or device or investigational therapy within 30 days before Screening.

4.4. Withdrawal Criteria

All participants have the right to withdraw at any point during the study without prejudice. Investigators can discontinue any participant at any time. Whether participant withdrawal is the decision of the participant, or an investigator, the following situations may occur:

1. The participant is withdrawn from study medication and the participant withdraws consent to release follow-up information.
2. The participant is withdrawn from study medication but all follow-up information can still be collected.
3. The participant is withdrawn from study medication temporarily, but then recommences, and all follow-up information is collected.

If one of these circumstances should occur, the management of the participant will be at the clinical discretion of his or her treating physician.

Because intention-to-treat analysis requires inclusion of all randomised participants in the analysis, it is important to obtain complete follow-up safety data for as many participants as possible whether or not they receive their assigned treatment or have discontinued the study drug. Every attempt will therefore be made to collect follow-up information except for those participants who specifically withdraw consent to release of such information.

The pain intensity, pain relief assessment and the subject's global evaluation of the study medication will be required to be collected by the time of early withdraw.

It will be documented whether or not each participant completed the clinical study. If for any reason the study treatment or observations were discontinued, the reason will be recorded and the Sponsor will be notified promptly.

5. TREATMENTS

5.1. Treatments to be Administered

5.1.1. *Identification and Description of Test Agents*

Treatment A	Maxigesic® IV IV acetaminophen 1000 mg and IV ibuprofen 300 mg /100 mL solution for infusion.
Treatment B	IV Acetaminophen 1000 mg/100 mL solution for infusion
Treatment C	IV Ibuprofen 300 mg/100 mL solution for infusion.
Treatment D	Placebo IV- 100 mL solution for infusion

All the study drug will be administered 6 hours (q6H) for 48 hours with a maximum of 4 doses within a 24 hour period.

5.2. Dosing Schedule and Instructions

Administration of the study drug will begin on the morning of the first postoperative day (Day 1) once the participant's eligibility has been confirmed by achieving a pain level of ≥ 40 mm VAS within the 9-hour qualification period after discontinuation of the continuous anesthetic infusion.

All study drugs will be administered by injection into a dedicated indwelling venous cannula, infused over 15 minutes. The study drugs will be administered every 6 hours (q6H) over the 48 hour treatment period (a total of 8 doses).

5.3. Storage and Handling of Study Drugs

All study drugs are manufactured by S.M. Farmaceutici S.R.L. located in Zona Industriale-85050 TITO (PZ) Italy, at their GMP approved manufacturing facility.

Maxigesic® IV, IV acetaminophen and IV ibuprofen solutions for infusions have been shown to be stable for 24 months when stored at 25^0C (77^0F).

The study drug supplied for this study is to be prescribed only by the Principal Investigator or named co-investigators and may not be used for any purpose other than that outlined in this protocol. Neither the investigators nor any designees may provide study drug to any participant not enrolled in this study.

The investigator or pharmacy designee will maintain an inventory record of the study drug dispensed to assure regulatory authorities and the Sponsor that the investigational drugs have not been dispensed to any person(s) who is not a participant of this study.

At the termination of the study, all unused study drugs (once they have been inventoried and the monitor has reviewed their accountability records) will be destroyed, and a destruction certificate will be issued by a licensed destruction company.

5.4. Rescue Medication

Subjects may receive supplemental analgesia with an opioid product (oxycodone 5 or 10 mg every 4-6 hours as needed) after surgery and before randomization to help control breakthrough pain if the regional anesthetic infusion fails to provide adequate anesthesia.

Though sites will be encouraged to use only the oxycodone as supplemental analgesia if adequate pain relief is not achieved with oral oxycodone, as a secondary rescue analgesia, 2-4 mg intravenous morphine sulphate will be allowed to be administered every 4 hours, as needed. If the regional anesthetic infusion and supplemental primary and secondary analgesia do not effectively control the subject's postoperative pain, then the subject will be discontinued from the study and pain will be managed per standard of care/investigator discretion.

After randomization, subjects will be encouraged to wait for at least 1 hour after the first dose of study drug before receiving first rescue medication to allow time for the study drug to exert its pharmacological effect. Rescue will not be restricted during this period if required.

The study drug will be administered as usual in addition to the rescue medication.

In the event of rescue medication use, a pain intensity assessment and pain relief assessment shall be performed prior to the administration of rescue medication and the time-adjusted SPID and TOTPAR will be calculated using this pre-rescue assessment.

6. STUDY ASSESSMENTS

6.1. Efficacy Assessments

6.1.1. *Pain Intensity Assessment*

Pain intensity assessment will be obtained by subjects mark on a 100 mm visual analogue scale (VAS) with 0 = No pain and 100 = Worst pain imaginable, and will be used to calculate the following efficacy assessment endpoints:

- Summed Pain intensity differences (SPID) (calculated as a time-weighted average) over 0 to 48 hours (SPID-48) after time 0
- Pain intensity difference (PID) at each scheduled time point after Time 0
- Pain intensity score at each scheduled time point
- SPID over 0-4 hours (SPID-4), over 0-8 hours (SPID-8), and over 0-24 hours (SPID-24) after Time 0

Pain intensity assessment on the VAS will be recorded in the inpatient subject diary at scheduled time points during the 6-hour period after Time 0 (5, 10, 15, 30 and 45 minutes, then 1, 1.5, 2, 3, 4, 5 and 6 hours) and then immediately before taking each dose of the study drug and 2 hours after each dosing while awake and at the end of 48 hours of double blind treatment period. If additional analgesia is required, Pain intensity assessment on the VAS will be recorded immediately before taking each dose of the rescue medication (Pre-rescue VAS assessment).

In the event of rescue medication the time-adjusted SPID up to the administration of rescue medication will be calculated.

6.1.2. *Pain Relief Assessment –Categorical 5 point Pain Relief Rating*

Pain relief assessment will be obtained by marking on the 5-point categorical rating scale with:

☐ 0= no pain relief; (the pain is the same, or worse, than the starting pain)

☐ 1=a little pain relief; (the pain is less than half gone)

☐ 2= some pain relief; (the pain is about half gone)

☐ 3= a lot of pain relief; (the pain is more than half gone)

☐ 4=complete pain relief; (the pain is completely gone)

Pain relief assessment on the 5-point categorical scale will be recorded in the inpatient subject diary at scheduled time points during the 6-hour period after Time 0 (5, 10, 15, 30 and 45 minutes, then 1, 1.5, 2, 3, 4, 5 and 6 hours) then immediately before taking each dose of the study drug and 2 hours after each dosing while awake and at the end of 48 hours of double blind treatment period. If additional analgesia is required, Pain relief assessment will be recorded immediately before taking each dose of the rescue medication (Pre-rescue pain relief assessment).

In the event of rescue medication the time-adjusted TOTPAR up to the administration of rescue medication will be calculated.

Pain relief assessment rating will be used to calculate the following endpoints:

- Summed pain relief (TOTPAR) (calculated as a time-weighted average) over 0-4 hours (TOTPAR-4), over 0-8 hours (TOTPAR-8), over 0-24 hours (TOTPAR-24) after Time 0, and over 0-48 hours (TOTPAR-48) after Time 0
- Pain relief sore on a 5-point categorical scale at each scheduled time point after time 0
- Peak pain relief
- Time to peak pain relief

6.1.3. *Time to Perceptible and Meaningful Pain relief (Two-stopwatch method)*

Time to onset of pain relief in minutes after the first dose of study drug is defined as (i) perceptible pain relief confirmed by (ii) meaningful pain relief as measured by the two-stopwatch method.

The two stopwatches will be started immediately after the intravenous infusion starts (the first dose of study medication. This is Time 0. Each participant will be instructed, "*Stop 'Stopwatch 1' when you first feel any pain relief whatsoever. This does not mean you feel completely better, although you might, but when you first feel any relief in the pain you have now*" (i.e. perceptible pain relief). The participant will also be instructed, "*Stop 'Stopwatch 2' when you feel the pain relief is meaningful to you*" (i.e. meaningful pain relief). If the participant does not press/stop the stopwatches within 6 hours after Time 0, the use of the stopwatches will be discontinued.

The two-stopwatch procedure will be used to calculate the following efficacy endpoints:

- Time to perceptible pain relief
- Time to meaningful pain relief

The methodology of two stopwatch procedures is presented in Appendix 6.

6.1.4. *Requirement of Rescue Analgesia*

Subjects may receive supplemental analgesia with an opioid product (oxycodone 5 or 10 mg every 4-6 hours as needed) after surgery and before randomization to help control breakthrough pain if the regional anesthetic infusion fails to provide adequate anesthesia.

Though sites will be encouraged to use only the oxycodone as supplemental analgesia if adequate pain relief is not achieved with oral oxycodone, as a secondary rescue analgesia, 2-4 mg intravenous morphine sulphate will be allowed to be administered every 4 hours, as needed. If the regional anesthetic infusion and supplemental primary and secondary analgesia do not effectively control the subject's postoperative pain, then the subject will be discontinued from the study and pain will be managed per standard of care/investigator discretion.

Participants will be encouraged to avoid rescue if their pain is mild in severity (i.e. less than 40 mm on the VAS pain intensity scale) and to wait up to 60 minutes after study drug administration, if possible.

The use of rescue medication will be documented on the inpatient subject diary and will be used to calculate the following efficacy endpoints:

- Proportion of subjects using rescue medication
- Time to first use of rescue medication (duration of analgesia)
- Total use of opioid rescue analgesia over 0-24 hours and 0-48 hours

6.1.5. *The Global Evaluation of Study Drug*

Participants will complete a patient's global evaluation of study drug at the end of treatment period (Day 3) before discharge from the study site.

Participants will be asked to "How do you rate the study medication?" on a 5 point categorical scale:

1 = Poor;

2 = Fair;

3 = Good;

4 = Very good;

5 = Excellent.

6.2. Safety Assessments

The safety endpoints are the incidence of treatment-emergent adverse events (AEs) and changes in vital measurements.

To rigorously evaluate the local tolerance to study medication at the infusion site, no other drug will be administered through the cannula dedicated to the infusion of the study drug.

7. EXPERIMENTAL PROCEDURE

7.1. Sequence of Procedures

An overview of the sequence of procedures and study assessments are summarised in Table 2, Schedule of Assessments.

Table 1: Schedule of Assessments

Measurements/Treatments	Screening Period (Days -28 to 0)	Day 0 (Day of Surgery)	Day 1-2 (post-surgery qualification and 48- hours study period) and Day 3 (discharge)	Follow –Up Phone Call (Day 7 ±2 Days)
Informed Consent	✓			
Inclusion/Exclusion Criteria	✓	✓		
Demographic Data	✓			
Complete Medical History	✓			
Physical Examination	✓	✓		
X ray (Foot 2 views)[1]	✓			
Concomitant Medications	✓	✓	✓	✓
Urine Pregnancy Test (females only)	✓	✓		
Urinalysis	✓			
Biochemistry & Haematology	✓			
Vital Signs	✓	✓	✓[5]	
Urine Drug Screening Test	✓			
Alcohol Breathalyzer Test		✓		
Surgery		✓		
Randomisation[2]			✓	
Study Drug Administration[3]			✓	
Pain Intensity Assessment			✓	
Pain Relief Assessment			✓	
Time to perceptible and meaningful pain relief			✓	
Global Evaluation of Study Drug [4]			✓	
Rescue medication and timing			✓	
AE Monitoring	✓	✓	✓	✓

[1] Radiographs taken within 6 months before Screening will be acceptable.
[2] Randomisation will occur within the 9 hour period after discontinuation of the anesthetic block which is approximately at 3AM on Day 1, when the pain intensity rating is ≥ 40 mm on the VAS.
[3] The first dose of the study drug will be administered once the participant is randomised and continues 6 hourly for up to 48 hours
[4] Done either at early termination or upon completion of the treatment period, prior to discharge from study centre.
[5.] Vital signs will be evaluated at Time 0 and following first dose infusion on Day 1, then each morning prior to the intravenous infusion and at discharge, early termination

7.1.1. *Screening Period (Day -28 to Day 0)*

Screening will occur up to 28 days prior to the day of surgery (Day 0).

Prior to the initiation of the screening assessments, potential participants will be given a complete explanation of the study.

Once an individual has agreed to participate and signed a copy of the Informed Consent documents the following evaluations will be performed to assess the participant's eligibility for enrolment in the study:

- Demographic data (age, sex, height, weight)
- Complete medical history - including past or present history of cardiac, pulmonary, gastrointestinal, hepatic, renal, immunological, haematological, neurological, musculoskeletal or psychiatric conditions (if any), allergy to food or drugs and medication history for the previous three months.
- Physical examination including the assessments of vital signs (heart rate, blood pressure, temperature, respiratory rate)
- Complete X-ray for the foot-2 view (Radiographs taken within 6 months before Screening will be acceptable)
- Recording of concomitant medications
- Urine pregnancy tests (females only)
- Urine analysis
- Urine Drug Screening Test (amphetamines, barbiturates, benzodiazepines, cocaine, methamphetamines, opiates, phencyclidine (PCP), and tetrahydrocannabinol (THC)
- Blood screening tests including:

➢ Haematology

- ✓ Haemoglobin
- ✓ Haematrocrit
- ✓ Platelet count
- ✓ Red Blood Cell (RBC) count
- ✓ White Blood Cell (WBC) count
- ✓ Differential Leukocyte Count (DLC)

- Biochemistry
  - ✓ Sodium
  - ✓ Potassium
  - ✓ Urea
  - ✓ Creatinine
  - ✓ Phosphate
  - ✓ Glucose
  - ✓ Albumin
  - ✓ Total protein
  - ✓ Alkaline phosphates
  - ✓ Gamma-glutamyl transferase
  - ✓ Aspartate transaminase
  - ✓ Alanine transaminase
  - ✓ Bilirubin

7.1.2. *Day of Surgery (Day 0)*

Subjects will be admitted to the study site on the morning of the scheduled surgery (Day 0), and will remain at the study site until postoperative Day 3 (a total of 3 nights at the study site).

On Day 0, subjects who continue to meet all study entry criteria will undergo standard first metatarsal bunionectomy procedure under a standardized regimen of regional anesthesia. The local anesthetic technique to be used for this surgery comprises a combination of a PSB to establish and maintain surgical field anesthesia and a continuous sciatic infusion to provide an effective method of controlling pain in the immediate postoperative period.

The PSB will be administered using modifications of the Singelyn technique (13). Subjects will receive midazolam and/or propofol for initial sedation at the anesthesiologist's discretion. After adequate sedation is achieved, the anesthesiologist will inject approximately 5 mL lidocaine 1% (plain) (or suitable short acting local anesthetic without epinephrine) locally to anesthetize the skin, and will determine the location of the sciatic nerve for the PSB using a nerve stimulator per standard technique. Once the appropriate location is determined, the anesthesiologist will inject 40 mL of ropivacaine 0.5% to establish the PSB. Subsequently a catheter will be placed in the proximity of the popliteal sciatic nerve for delivery of postoperative anesthesia. If the PSB is not sufficient to provide adequate intraoperative anesthesia, a standard Mayo block may be established using lidocaine 2% (plain) not to exceed 25 mL. The time, date, dose, and route of all local anesthetics will be recorded in the CRF.

The regional anesthesia will be continued postoperatively via a continuous anesthetic infusion. Subjects may receive supplemental analgesia with an opioid product (see below) after surgery

and before randomization to help control breakthrough pain if the regional anesthetic infusion appears to be ineffective in the opinion of the investigator.

If the regional anesthetic infusion and supplemental analgesia do not effectively control the subject's postoperative pain, then the subject will be discontinued from the study.

7.1.3. *Randomisation (Day 1 – First postoperative day)*

On Day 1, the regional anesthetic infusion will be discontinued at approximately 3AM. When subjects request pain medication, they will be asked to rate their pain intensity using the 100 mm Visual Analogue Scale (0-100).

During the 9-qualification hour period after discontinuation of the anesthetic block, subjects who experience a pain intensity rating of ≥ 40 mm on the VAS are eligible to be enrolled into the study.

If their pain intensity ratings do not meet the minimum entry criteria within 9 hours of discontinuation of the regional anesthesia, subjects will not be eligible for enrollment and will receive routine postoperative care at the investigator's discretion.

Once the pain intensity entry criteria are met, subjects will be randomly assigned to one of the 4 treatment groups:

Treatment A	Maxigesic® IV IV acetaminophen 1000 mg and IV ibuprofen 300 mg/100 mL solution for infusion.
Treatment B	IV Acetaminophen 1000 mg/100 mL solution for infusion
Treatment C	IV Ibuprofen 300 mg in 100 mL infusion.
Treatment D	Placebo IV – 100 ml solution for infusion

Study drug will be administered as a blinded medicine. Study drug will be administered by injection into a dedicated indwelling venous cannula, infused over 15 minutes every 6 hours (q6h regimen) for 48 hours after the first dose, with a maximum of 8 doses.

7.1.4. *Treatment Period (Day 1-3)*

The treatment period will commence at the start of study drug administration and conclude at approximately 48 hours after the first dose (with a maximum of 8 doses).

The following participant reported measurements will be taken during the treatment period:

- Pain Intensity Assessment on the 100 mm VAS will be collected at the following times:

- 5,10,15, 30, 45 minutes, 1, 1.5, 2, 3, 4, 5, 6 hours after the first dose of the study drug
- immediately before taking each dose of the study drug and 2 hours after each dosing while awake.
- At the end of 48 hours of double blind treatment period
- immediately before taking each dose of the rescue medication if additional analgesia is required.

➢ Pain Relief Assessment on a 5-point categorical rating will be collected at the following time points:

- 5, 10, 15, 30, 45 minutes, 1, 1.5, 2, 3, 4, 5, 6 hours after the first dose of the study drug
- immediately before taking each dose of the study drug and 2 hours after each dosing while awake.
- At the end of 48 hours of double blind treatment period
- immediately before taking each dose of the rescue medication if extra pain relief is required.

➢ Time to onset of perceptible and meaningful pain relief after the first study drug administration, using the two-stopwatch method (described in section 6.1.2) during the first dosing period

➢ The time of the first dose of rescue medication administered during the 48 hour treatment period

➢ The amount of rescue medication administered during the 48 hours treatment period

➢ Patient's global evaluation of study drug at the end of 48 hours treatment period

➢ Vital signs will be taken at T0, following the first dose infusion, then prior to the first infusion each morning, and at discharge/early termination

Subjects may receive supplemental analgesia with an opioid product (oxycodone 5 or 10 mg every 4-6 hours as needed) after surgery and before randomization to help control breakthrough pain if the regional anesthetic infusion fails to provide adequate anesthesia.

Though sites will be encouraged to use only the oxycodone as supplemental analgesia if adequate pain relief is not achieved with oral oxycodone, as a secondary rescue analgesia, 2-4 mg intravenous morphine sulphate will be allowed to be administered every 4 hours, as needed. If the regional anesthetic infusion and supplemental primary and secondary analgesia do not effectively control the subject's postoperative pain, then the subject will be discontinued from the study and pain will be managed per standard of care/investigator discretion.

During the treatment period, subjects will be encouraged to wait for at least 1 hour after the first dose of study drug before receiving first rescue medication to allow time for the study drug exert its pharmacologic effect.

During the treatment period, subject whose pain cannot be adequately managed by a combination of study drug and rescue medication, or who develop unacceptable side effects during the study, will be discontinued from further study participation. Their pain will be managed conventionally at investigator's discretion. Pain intensity, pain relief assessments and Subject's global evaluation of study medication will be required to be completed prior to premature study termination.

Before discharge from the study site on Day 3, study personnel will dispense a prescription for pain medication (if not already dispensed). During the follow-up phone call, subjects will also be asked about any additional AEs that have occurred since discharge.

7.1.5. *Follow-up (5 -9 days after surgery)*

A final follow-up phone call will be conducted within 5-9 days after the surgery. At this follow-up call any additional adverse event and concomitant medication data will be collected.

8. ADVERSE EVENTS

Participants experiencing adverse events will be followed clinically until their health has returned to baseline status or until all abnormal values have returned to normal or have otherwise been explained. The investigators will provide or arrange appropriate supportive care for the participant if necessary.

Adverse events common to acetaminophen and ibuprofen are listed in Appendix 2.

8.1. Definitions

8.1.1. *Adverse Event*

An adverse event (AE) is defined as any unintended, unfavourable clinical sign or symptom, any new illness or disease or deterioration of existing illness or disease, or any clinically relevant deterioration in laboratory variables (e.g., haematological, biochemical, hormonal) or other clinical tests (e.g., ECG), whether or not considered treatment related.

Note that the definition could include accidents and the reasons for changes in medicine (drug and/or dose), medical, nursing and/or pharmacy consultation, and admission to hospital or surgical operations.

Normal postoperative sequelae, including pain, itching, bruising, numbness, bleeding, burning, tingling, and edema at the surgical site, will not be recorded as AEs unless they are of greater severity and/or intensity than would be expected in the surgeon/investigator's opinion.

Planned hospital admissions and/or surgical operations for an illness or disease which existed before the drug was given or the participant was randomised in a clinical study will not be considered adverse events.

The severity of an adverse event and the relationship to study medication will be assessed by the investigator (see Appendix 1).

8.1.2. *Serious Adverse Event*

A serious adverse event is an AE (at any dose of study drug) that:

- results in death;
- is life-threatening (i.e., the participant was, in the opinion of the investigator, at immediate risk of death from the event as it occurred; this does not include an event that, had it occurred in a more severe form, might have caused death);
- results in persistent or significant disability/incapacity;
- requires in-participant hospitalization or prolongs hospitalization;
- is a congenital anomaly/birth defect; or
- is another medically significant event that, on the basis of appropriate medical judgment, may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g. allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse).

An adverse event fulfilling any one or more of these criteria must be reported as a serious adverse event. The circumstances surrounding the occurrence of the event must be gathered, however the event itself must be reported, irrespective of the circumstances.

A distinction should be drawn between serious and severe adverse events. Severity is an estimate or measure of the intensity of an adverse event, while the criteria for serious are indications of adverse participant outcomes for regulatory reporting purposes. A severe adverse event need not necessarily be considered serious and a serious adverse event need not be considered severe. For example, nausea that persists for several hours may be considered severe nausea, but not a serious adverse event. On the other hand, a myocardial infarction that may be considered minor could also be a serious adverse event if it prolonged hospitalization, for example.

8.2. Procedure for Adverse Event Reporting

All adverse events (non-serious and serious) spontaneously reported by the participant and/or in response to an open question from the study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded. All adverse events (non-serious and serious) must be recorded on the source documents and case report forms provided by the Sponsor.

8.3. Procedure for Serious Adverse Event Reporting

8.3.1. *Reporting to Sponsor*

In addition to entering each SAE irrespective of causality on the appropriate page of the Case

Report Form (CRF), the investigator must complete a Serious Adverse Event Report (SAER) for each serious adverse event regardless of causality to study drug. The SAER must be faxed to the Drug Safety Officer at AFT Pharmaceuticals Ltd within 24 hours (from the point in time when the SAE is realised) to +64 9 4880234. The Drug Safety Officer will contact the investigator should it be necessary to clarify any of the event information. The investigator should provide any additional follow-up information for the event to AFT Pharmaceuticals Ltd as soon as it becomes available and up to the point the event has been resolved. This reporting requirement is applicable to serious adverse events that occur during the designated study period. If the investigator is notified of a serious event post study that he or she determines to be causally related to study medication, the event should also be reported through this process.

8.3.2. *Reporting to Local EC/IRB*

All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting to local ethics committee with 72 hours of the study staff being notified (or being made aware). The report shall be in compliance with local ethics committee requirements.

Expedited reporting is in appropriate for serious events from clinical investigations that are considered not related to study product, whether the event is expected or not. Similarly, non-serious adverse reactions, whether expected or not, will not be subject to expedited reporting. However, these adverse reactions and adverse event will be included in the periodic safety reports to local ethics committee.

The sponsor shall take the responsibility to continually monitor the safety of its clinical development program and advise local ethics committee in a prompt manner if the updated safety information impacts the continued ethical acceptability of the trial which indicates the need for a change in the trial protocol or participant information statement.

8.3.3. *Reporting to Regulatory Agencies*

The Principal Investigator shall notify the regulatory agencies (US FDA) by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than 7 calendar days (21 CFR 312.32) after the sponsor's initial receipt of the information. Each written notification may be submitted on FDA Form 3500A or if preferred on a CIOMS I form (21 CFR 312.32).

The IND safety reporting to Regulatory Agencies will follow the Guidance for Industry and Investigators-Safety Reporting Requirements for INDs and BA/BE Studies (US FDA CDER, CBER December 2012).

8.4. Data Safety Management Board (DSMB) Review:

No DSMB reviews are planned for this study.

9. PLAN FOR STATISTICAL AND OTHER CALCULATIONS

This study is a Phase III, placebo-controlled randomised, double-blind, parallel-design trial of

four treatment regimens, to examine the difference in analgesia between Maxigesic® IV, the individual constituents and placebo.

9.1. Analyses Populations

The analysis populations include the following:

- The Intent-to-treat population (ITT) will consist of all subjects who receive at least 1 dose of study drug. Subjects will be included in the group to which they were randomised irrespective of the treatment actually taken. The ITT population is the primary population for the efficacy analysis.

- The Per-protocol (PP) Population will consist of all ITT subjects who remain in the study for at least 48 hours of treatment (complete the 48 hour treatment period) and who do not incur a major protocol violation that would challenge the validity of their data. This population may be utilized to evaluate the sensitivity of the primary efficacy analysis.

- The PP population will be used for secondary analyses of the primary and secondary efficacy outcomes, if this population is less than 90% of the ITT population.

- The safety population will include all subjects who are treated with study drug (ITT). Subjects will be included in the treatment group according to the treatment actually taken. The safety population is the population for all safety assessments.

9.2. Sample Size

In total, 275 participants (75 in each active group and 50 in placebo) will be randomised into the study. This sample size will provide 80% power to detect as statistically significant (2-sided α=0.05) any difference >10.5mm [ES=0.6] in mean time-adjusted SPID between Maxigesic® IV and each of the three comparator study groups.

9.3. Statistical Analyses

9.3.1. *Efficacy Analysis*

The analysis of the primary efficacy endpoint SPID-48 (calculated as a time-weighted average) will be performed using an analysis of covariance (ANCOVA) model, which will include treatment effect as the fixed factor and baseline pain intensity as a covariate.

The primary efficacy endpoint will compare IV Maxigesic® with each of the three comparators using a sequential testing strategy to preserve the two-sided type I error rate at α=0.05. The pairwise comparisons will be conducted in the following sequence with the sequence of tests only continuing if the preceding test is statistically significant at $p<0.05$. The pairwise comparisons with IV Maxigesic® will be conducted in the following sequence: 1. Placebo IV, 2. IV acetaminophen, and 3. IV ibuprofen.

Other comparisons between the treatment groups will be considered secondary, and no further

adjustments for multiple comparisons will be implemented. The least-squares estimates of the means for each treatment group from the ANCOVA model will be tabled with standard errors and the mean differences between treatments will be summarised with 95% confidence intervals. Secondary analyses may explore the consistency of treatment effects across gender, ethnicity and surgical trauma rating groups by including these as covariates in addition to baseline pain intensity. The primary efficacy variable will also be summarized by site, with no formal statistical comparisons between sites.

The continuous secondary endpoints such as SPID-6, SPID-12, SPID-24, pain intensity score (VAS) at each scheduled time point, pain intensity difference (PID) at each scheduled time point TOTPAR-6, TOTPAR-12, TOTPAR-24 and TOTPAR-48 will be summarised by treatment group using means, standard errors medians, minima, and maxima. These endpoints will analysed using ANCOVA models with the relevant baseline assessment as a covariate and these results summarised as the mean differences between treatments with 95% confidence intervals.

The ordinal secondary endpoints: pain relief score at each scheduled time point, peak pain relief, total dose of rescue medication and patient's global evaluation of study drug will be summarised by treatment group using the number and percentage of subjects within each category for each treatment group, medians and inter-quartile ranges as appropriate.

Nominal P values from Mann-Whitney U tests and chi-square tests comparing the Maxigesic IV group with each treatment group will be provided, but no formal statistical inferences will be drawn on the basis of these tests.

The time-to-event endpoints: onset of analgesia, use of rescue medication and time to peak relief will be summarised for each treatment group using the Kaplan-Meier method. Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief) will be based on data collected using the two-stopwatch method following the first dose of study drug. This will be right-censored at 6 hours for subjects who do not experience both perceptible pain relief and meaningful pain relief during the 6-hour interval or who require rescue medication prior to achieving perceptible or meaningful pain relief.

The time to event results will be summarised by treatment group as the number of subjects analyzed, the number of subjects censored, the median times to event (if attained) with 95% confidence intervals (CIs). Additionally, the Kaplan-Meier estimates of the percentage with effective analgesia at 6 hours with 95% confidence intervals will be calculated. Log-rank tests will also be used to compare the Maxigesic IV group with each of the comparators for the time-to-event outcomes.

The proportion of subjects using rescue medication will be analysed using a logistic regression model that includes baseline pain intensity as a covariate. This model will be used to evaluate the treatment effect and summarise the odds ratios and 95% confidence intervals comparing Maxigesic with the three comparator groups.

Baseline values for all relevant outcomes are defined as the last measurements taken before Time 0.

9.3.2. *Safety Analysis*

Data listings will be provided for protocol-specified safety data. The Medical Dictionary for Regulatory Activities (MedDRA) (Version 9.1 or higher) will be used to classify all AEs with respect to system organ class and preferred term. Adverse event summaries will include only treatment-emergent AEs, which will be summarized for each treatment group. Fisher's 2-sided exact test may be used to compare the rates of occurrence of the more common treatment-emergent AEs (>10% in total group) between the Maxigesic® IV group and the three comparator groups.

For vital sign measurements, descriptive statistics will be provided at each scheduled time point for each treatment group. Changes from Baseline for vital signs will be calculated for each subject, and descriptive statistics will be provided on changes in vital signs from baseline for each treatment group at each scheduled time point after Baseline. No formal statistical tests will be performed.

9.4. Demographic and Background Characteristics

Demographic and baseline characteristics (including age, gender, race, weight, height, BMI, medical history, surgery duration, and baseline pain intensity) will be summarized for each treatment group and for the overall population using descriptive statistics including means, medians, standard deviations, ranges and frequencies and percentages as appropriate. No formal statistical analyses will be performed.

9.5. Missing Data

Pain intensity or relief assessments with sporadic missing data points not due to early withdrawal will have these intermediate points interpolated and be time-adjusted if necessary to allow analysis of the efficacy endpoints.

As the full study is conducted within the trial clinics it is anticipated that there will be very few individuals who do not complete the full 48 hour efficacy assessments even if some withdraw from study medication. For pain intensity and relief measures, any subjects who withdraw from the study early e.g. due to lack of efficacy, an AE or intolerance to study drug, but have post withdrawal assessments, all their scheduled assessments after the time of withdrawal will be included in the ITT population for the primary efficacy endpoint analysis. The data from those who withdraw consent to participant in the study and therefore provide incomplete efficacy data will be imputed as detailed below.

It is expected that these early withdrawals will have higher pain intensity and lower relief measures therefore these poor outcomes will be manifest in the efficacy measures. Diligent monitoring and data review will be implemented before database lock to ensure that the reasons for withdrawal are correctly identified.

For participants who withdraw from all study procedures (e.g. following an AE) and therefore provide no additional efficacy data beyond the point of withdrawal the relevant efficacy data will

be imputed using a multiple imputation process. The imputation model will include the baseline measures age, gender and the baseline efficacy measure additionally the post randomisation measures of the appropriate efficacy outcome, randomised group and the interaction between the post-randomisation efficacy outcome and randomised group.

For subjects who take any dose of rescue medication, a 6 hour window of subsequent measures after the dose of rescue medication will be imputed using the assessment which is taken immediately prior to the use of rescue medication. It is expected that the assessment immediately prior to the use of rescue will reflect the high pain intensity level and poor relief necessitating the use of rescue medication therefore, these poor outcomes will be manifest in the efficacy measures.

Sensitivity analyses will be undertaken on all pain intensity and pain relief outcomes which only include measured data without any imputation. The results from these analyses will be used to show the sensitivity of the results to the imputation process.

9.6. PROCEDURE FOR AMENDMENTS TO STATISTICAL PLAN

It is intended that all statistical analyses specified in this protocol will be performed. However, it is conceivable that some scheduled analyses may not be performed. In addition, study observations or analysis results may suggest the need for additional statistical analyses of the collected study data. In either case, deviations (subtractions or additions) from the planned statistical analysis will be fully described in the final clinical study report.

9.7. DATA COLLECTION

The CRF will be used to collect all participant data assessments that will be used for evaluation of specified analyses. The CRF should be completed in a timely fashion.

As this study will be conducted under International Conference on Harmonization (ICH) GCP guidelines, these guidelines require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- A period of at least 2 years following the date after the last approval of a marketing application in an ICH region and until there are not any pending or contemplated marketing applications in an ICH region.
- A period of at least 2 years after the formal discontinuation of clinical development of the investigational product.

Should countries participating in this study have other guidelines for record retention, the period of record retention should follow the strictest guidelines, for example, New Zealand guidelines require documents to be retained for 10 years and Australian guidelines for 15 years.

It is agreed that the investigator and the Sponsor will share in the responsibility to maintain these records. Each will maintain a complete set. Neither the investigator not the Sponsor will dispose of any records relevant to this study without either written permission from the other and from the relevant authorities. The investigator and Sponsor shall both be responsible for maintaining adequate and accurate hard copy source documents of all observations and data generated during

this study, including any data clarification forms (DCFs) received from the Sponsor. Such documentation is subject to inspection by the Sponsor or its agents, and/or regulatory agencies. The investigator may work with the sponsor to ensure that archiving facilities are provided during the archiving period.

10. STUDY OR STUDY SITE TERMINATION AND PARTICIPANT DISCONTINUATION

10.1. STUDY OR STUDY SITE TERMINATION

If the Sponsor, Investigator, Study Monitor or appropriate regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the study centre should be terminated, this action may be taken after appropriate consultation among the Sponsor, Investigator and Study Monitor. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the participants enrolled in the study.
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

A study conducted at a single study site or a single study site in a multi-center study may also warrant termination under the following conditions:

- Failure of the Investigator to enrol participants into the study at an acceptable rate.
- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities.
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor or appropriate regulatory authority.
- Insufficient adherence to protocol requirements.

Study termination and follow-up will be performed in compliance with the conditions set forth in the International Conference of Harmonisation (ICH) sixth efficacy publication (E6) on Good Clinical Practice, Section 4.12, ICH E6 4.13, ICH E6 5.20 and ICH E6 5.21.

10.2. PARTICIPANT DISCONTINUATION

Participants will be encouraged to complete the study; however, they may voluntarily withdraw at any time. The Investigator will provide a written report on the appropriate CRF page describing the reason for discontinuation. If a participant withdraws before completion this will be dealt with as described in Section 4.4.

A participant may be removed from the study for the following medical or alternative reasons:

- Adverse event
- If a participant suffers an adverse event that, in the judgement of the Investigator or the Sponsor, presents an unacceptable consequence or risk to the participant, the participant may be discontinued from further participation in the study.

- Intercurrent illness
- A participant may also be discontinued from the study if, in the judgement of the Investigator, he or she develops an intercurrent illness or complication that is not consistent with the protocol requirements or that, in any way, justifies his or her withdrawal from the study.
- Failure of subject to comply fully with protocol required safety and/or efficacy assessments or general protocol non-compliance (in the opinion of the investigator at his/her discretion)

11. PROTOCOL DEVIATIONS

This study will be conducted, within reasonable limits, as described in this protocol, except for emergency situations in which the protection, safety, and well-being of the participant requires immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact the Sponsor, or the Sponsor's agent, at the earliest possible time by telephone. This will allow an early joint decision regarding the best way to proceed with the study (note the ITT protocol – it is expected that all consenting participants will at least continue to be followed up for adverse events). The investigator and the Sponsor will document this decision. The Institutional Review Board (IRB) or Ethics Committee (EC) will be informed of all protocol changes by the investigator in accordance with the IRB or EC established procedure. No significant planned or deliberate deviations from the protocol of any type will be made without the Sponsor's agreement and complying with all the IRB or EC established procedures.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. MONITORING

The Sponsor has ethical, legal, and scientific obligations to carefully follow this study in a detailed and orderly manner in accordance with established research principles and applicable regulations. As part of a concerted effort to fulfil these obligations the Sponsor's monitor will visit the centre(s) during the study in accordance with the Monitoring Plan set forth for this trial as well as maintain frequent telephone and written communication. The investigator expects that the Sponsor will fulfil this obligation, and provide early opportunity for the investigator to correct any deficiencies identified in the data.

12.2. AUDITING

The Sponsor can conduct audits at the study centre(s). Audits can include, but not be limited to: drug supply, presence of required documents, the informed consent process, and comparison of case report forms with source documents. The investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also audit the investigator during or after the study. The investigator should contact the Sponsor immediately if this occurs, and must fully cooperate with regulatory authority audits conducted at a reasonable time in a reasonable manner.

The sponsor agrees to meet all reasonable costs that arise out of such audits, including reasonable remuneration of staff involved in complying with the requirements of such audits.

13. ETHICS AND RESPONSIBILITY

This study will be conducted in compliance with the protocol, with the Sponsor's standard operating procedures and/or guidelines, the ICH GCP guidelines, the Declaration of Helsinki, and with any local country GCP guidelines, whichever are the strictest.

13.1. INFORMED CONSENT

Written informed consent will be obtained from the participant before any study-related procedures (including any pre-treatment procedures) are performed. The investigator(s) has both ethical and legal responsibility to ensure that each participant being considered for inclusion in this study, is given a full explanation of the protocol. This shall be documented on a written informed consent form, which shall be approved by the same IRB or EC responsible for approval of this protocol. Each informed consent form shall include the elements required by ICH GCP guidelines. The investigator agrees to obtain approval from the Sponsor of any written informed consent form used in the study, preferably prior to submission to the IRB or EC.

Once the appropriate essential information has been provided to the participant and fully explained by the investigators (or a qualified designee) and it is felt that the participant understands the implications of participating, the participant and the investigator (or a medically qualified designee) shall sign the IRB- or EC-approved written informed consent form. The participants shall be given a copy of the signed informed consent form, and the original shall be kept in the site's regulatory file. A second copy may be filed in the participant's medical record, if allowed by the institution.

13.2. INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE

This protocol and the written informed consent form shall be submitted to the IRB or EC identified with this responsibility at the research facility. Notification in writing of approval must come from the IRB or EC chairman or secretary, to the investigator, either as a letter or as a copy of the appropriate section of the IRB or EC meeting minutes where this protocol and associated informed consent form were discussed. The investigator will not participate in the decision. If the investigator is an IRB or EC member, the written approval must indicate such non-participation. The investigator will submit status reports to the IRB or EC at least annually (when applicable). The IRB or EC must be notified by the investigator in writing of the interruption and/or completion of the study; the investigator must promptly report to the IRB or EC all changes in research (protocol amendments) and will not make such changes without IRB or EC approval except where necessary to eliminate apparent immediate hazards to human participants. In these cases, the IRB or EC must be notified within 5 days of the change. The investigator will promptly report to the IRB or EC all unanticipated problems involving risk to participants or others. The investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB or EC and must agree to share all such documents and reports with the Sponsor.

13.3. GOVERNANCE OF STUDY AND PUBLICATION POLICY

The Governance of the study will be the joint responsibility of the Principal Investigators and the Sponsor.

The sponsor agrees that no restriction will be placed on publication of the data. The investigator agrees that the sponsor has the right to review and comment on any manuscript prior to submission for either publication or presentation at a scientific conference. Thirty days will be allowed for this review and comment.

The study will be registered by the Sponsor on the appropriate Clinical Trial Register.

14. CONFIDENTIALITY

All information generated in this study must be considered highly confidential and must not be disclosed by either the investigator or the Sponsor to any persons not directly concerned with the study without written prior permission from the Sponsor and Investigator (as the case may be). However, authorised regulatory officials, the Investigator personnel and Sponsor personnel will be allowed full access to the records. All medications provided and participant bodily fluids and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor and the Investigator, and in compliance with all relevant regulations.

Only initials and unique participant numbers in case report forms will identify participants. Their full names may, however, be made known to a regulatory agency or other authorised official if necessary and approved by the IRB or EC.

15. INVESTIGATOR AGREEMENT

Certain responsibilities devolve to the Principal Investigator (notably those of signing the Statutory Declarations related to the Ethics Committee, the requirement to retain records, and oversight and governance of the study). Other responsibilities apply to all named co-investigators.

I have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal, and scientific information necessary to conduct this study. I will personally conduct the study as described, with the assistance of co-investigators and study personnel.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel responsible to me who will participate in the study. Together with the Sponsor, I will arrange briefing sessions and will discuss the protocol with them, to assure myself that they are appropriately informed regarding the investigational new drug Maxigesic® IV, the concurrent medications, the efficacy and safety parameters and the conduct of the study in general. I agree to make all reasonable efforts to adhere to the attached protocol. I understand that this EC approved protocol will be submitted to the regulatory authorities by the Sponsor's Contractor, as appropriate. I agree to allow Sponsor monitors and auditors full access to all medical records at the research facility for participants screened or randomised in the study. In return the Sponsor agrees to undertake audits regularly and assist me in identifying any deficiencies in the conduct of the study as early as possible, and in instituting appropriate measures to address these.

I agree to provide all participants with informed consent forms, as required by government and ICH regulations. I further agree to report to the Sponsor any adverse experiences in accordance with the terms of this protocol and FDA regulation, 21 CFR 312.64.

Principal Investigator 's Name (printed)	Signature	Date

16. REFERENCES

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Appendix 1: Grading of Adverse Events

Severity:

Mild	Discomfort noticed but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect daily activity
Severe	Inability to work or perform daily activity

Relationship:

Not related	A temporal (timely) relationship of the onset of the event, relative to the administration of the product is unlikely or not reasonable. Or where another cause can explain the occurrence of the event by itself
Unlikely	A temporal (timely) relationship of the onset of the event, relative to the administration of the product is unlikely but cannot be ruled out.
Possibly related	A temporal (timely) relationship of the onset of the event, relative to the administration of the product is reasonable, but the event could have been due to an equally likely cause.
Probably related	A temporal (timely) relationship of the onset of the event, relative to the administration of the product is reasonable and the event is more likely to be explained by the medicinal product than by another cause.
Definitely related	A temporal (timely) relationship of the onset of the event, relative to the administration of the product is reasonable and there is no other cause to explain the event. Cause to explain the event, or a re-challenge is positive.

Appendix 2: Adverse Drug Reactions of the Investigational Product

Known adverse drug reactions of acetaminophen alone:

Impaired liver function or a history of liver disease:
Acetaminophen should be administered with caution to participants with impaired hepatic function because of the possibility of delayed elimination or increased serum concentrations.

Impaired Renal Function:
Acetaminophen should be administered with caution to participants with impaired renal function because of the possibility of delayed elimination or increased serum concentrations.

Known adverse drug reactions of Ibuprofen alone:

Asthma:
Caution is required if ibuprofen is administered to participants suffering from, or with a previous history of, bronchial asthma since ibuprofen has been reported to cause bronchospasm in such participants.

Ophthalmological Monitoring:
Adverse ophthalmological effects have been observed with NSAIDs; accordingly, participants who develop visual disturbances during treatment with ibuprofen should have an ophthalmological examination.

Impaired Liver Function or a History of Liver Disease:
Participants with impaired liver function or a history of liver disease who are on long term ibuprofen therapy should have hepatic function monitored at regular intervals. Ibuprofen has been reported to have a minor and transient effect on liver enzymes.
Severe hepatic reactions, including jaundice and cases of fatal hepatitis, though rare, have been reported with ibuprofen as with other NSAIDs. If abnormal liver tests persist or worsen, or if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), ibuprofen should be discontinued.

Impaired Renal Function:
Caution should be used when initiating treatment with ibuprofen in participants with considerable dehydration.
The two major metabolites of ibuprofen are excreted mainly in the urine and impairment of renal function may result in their accumulation. The significance of this is unknown. NSAIDs have been reported to cause nephrotoxicity in various forms; interstitial nephritis, nephrotic syndrome and renal failure. In participants with renal, cardiac or hepatic impairment, those taking diuretics and ACE inhibitors and the elderly, caution is required since the use of NSAIDs may result in deterioration of renal function. The dose should be kept as low as possible and renal function should be monitored in these participants.

Cardiovascular Effects:
Fluid retention and oedema have been reported in association with ibuprofen, therefore, the drug should be used with caution in participants with a history of heart failure or hypertension.

Aseptic Meningitis:
Aseptic meningitis has been reported only rarely, usually but not always in participants with systemic lupus erythematosus (SLE) or other connective tissue disorders.

Haematological Monitoring:
Blood dyscrasias have been rarely reported. Participants on long-term therapy with ibuprofen should have regular haematological monitoring.

Coagulation Defects:
Like other NSAIDs, ibuprofen can inhibit platelet aggregation. Ibuprofen has been shown to prolong bleeding time (but within the normal range), in normal participants. Because this prolonged bleeding effect may be exaggerated in participants with underlying haemostatic defects, ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anti-coagulation therapy.

Masking Signs of Infection:
As with other drugs of the NSAID class, ibuprofen may mask the usual signs of infection.

Special Precautions:
In order to avoid exacerbation of disease or adrenal insufficiency, participants who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

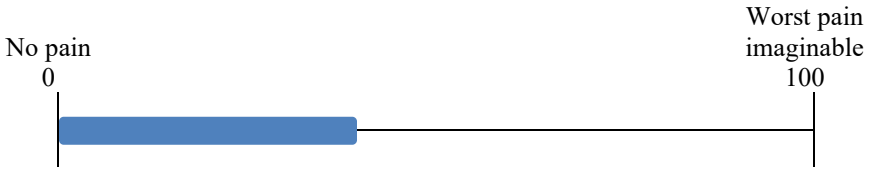
Appendix 3: Pain Assessment –100 mm VAS

100 mm Visual Analogue Scale

Mild Pain

Mild pain is annoying; it hurts, but might not really bother you and doesn't prevent you from doing things you might want to do. You would still be able to read a book or the newspaper and you would not automatically want to take medication.

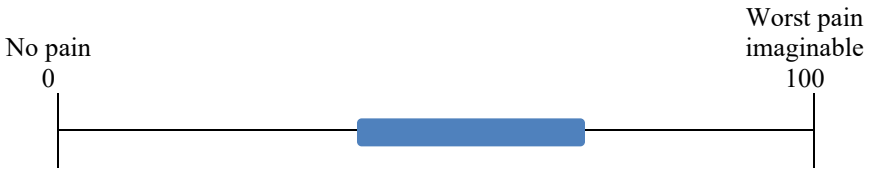
If you have mild pain you would mark in the shaded area below.



Moderate Pain

Moderate pain is uncomfortable and might make it hard to concentrate i.e. it is hard to ignore and it would be difficult to concentrate on reading a book or newspaper. It bothers you significantly and you want to relieve it by taking medication or doing something.

Moderate pain is represented on the pain scale by the shaded area below.



Severe Pain

Severe pain means your pain is intense and overwhelming. You would not be able to concentrate and can't think of anything other than your pain. You will definitely want and need medication to relieve it.

Appendix 4: Pain Relief Assessment –Categorical 5-Point Pain Relief Rating Scale

Please rate your pain relief:

☐ 0= no pain relief; (the pain is the same, or worse, than the starting pain)

☐ 1=a little pain relief; (the pain is less than half gone)

☐ 2= some pain relief; (the pain is about half gone)

☐ 3= a lot of pain relief; (the pain is more than half gone)

☐ 4=complete pain relief; (the pain is completely gone)

Appendix 5: Patient's Global Evaluation of Study Drug

How do you rate the study medication?

☐ 1= Poor;

☐ 2=Fair;

☐ 3=Good;

☐ 4=very Good;

☐ 5= Excellent

The assessment will be conducted at the end of 48 hours.

Appendix 6: Two Stopwatch Pain Relief Assessments

1. Start the two stopwatches immediately after the intravenous infusion starts (the first dose of study medication). This is Time 0.
2. Check both stopwatches have started, then supply "Stopwatch A" to the participant. Instruct the participant to **"stop 'Stopwatch A'** ***when you first feel any pain relief whatsoever. This does not mean you feel completely better, although you might, but when you first feel any relief in the pain you have now*****"** (Perceptible Pain Relief).
3. If/when the participant stops 'Stopwatch A' record time on stopwatch below:

Time of stopping the Stopwatch A (hh:mm:ss) (Perceptible Pain Relief) |____|____| : |____|____|: |____|____|

4. Ask the participant **"*Do you consider the pain relief you experienced meaningful*"**. Record answer below:

Is pain relief meaningful to the participant?	☐ Yes / ☐ No

5. If the participant answers "yes", the two stopwatch method is complete. Remove both Stopwatch A and B.
6. If the participant answers "no", instruct the participant to **"stop 'Stopwatch B'** ***when you feel the pain relief is meaningful to you*****"**.
7. If/when the participant stops 'Stopwatch B' record the time on the stopwatch below:

Time of stopping the Stopwatch B (hh:mm:ss) (Meaningful Pain Relief) |____|____| : |____|____|: |____|____|

NOTE:

1. If the subject never experiences "Perceptible Pain Relief", they will retain 'Stopwatch A' for the entire 6 hour evaluation period. If the subject experiences "Perceptible Pain Relief" but not "Meaningful Pain Relief", they will retain 'Stopwatch B' for the remainder of the evaluation period. Unless "Meaningful Pain Relief" is achieved, either by answering "yes" to the question or stopping 'Stopwatch B", the participant will always have an active stopwatch with them.
2. The two stopwatches will be discontinued if rescue medication is required.