STUDY TITLE:	A Phase 3, Open-Label, Multiple-Dose, Single-Arm Exposure Study of Maxigesic® IV in Patients with Acute Pain Following Orthopedic, General or Plastic Surgery
PROTOCOL IDENTIFICATION:	AFT-MXIV-11
NAME OF STUDY DRUG:	Maxigesic® IV
INDICATION STUDIED	Analgesia for acute postoperative pain
DEVELOPMENT PHASE:	Phase 3
IND APPLICATION NUMBER	124213
TRIAL REGISTRATION NUMBER:	ACTRN12619000587101p
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DATE:	21 Aug 2019

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:	A Phase 3, Open-Label, Multiple-Dose, Single-Arm Exposure Study of Maxigesic® IV in Patients with Acute Pain Following Orthopedic, General or Plastic Surgery
PROTOCOL NUMBER:	AFT-MXIV-11
DOCUMENT DATE:	21st Aug 2019

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Approved by		
Hartley Atkinson Managing Director	Signature:	Date: 21st Aug 2019

PROTOCOL SYNOPSIS

Name of Sponsor	AFT Pharmaceuticals Ltd
Name of Active Ingredient(s)	Acetaminophen and Ibuprofen
Title of Study	A Phase 3, Open-Label, Multiple-Dose, Single-Arm Exposure Study of Maxigesic® IV in Patients with Acute Pain Following Orthopedic, General or Plastic Surgery
Study Centers	Chesapeake Research Group 8030B Ritchie Highway Pasadena, MD 21122 United States of America Ph: +1 410 761 0118, Fax: +1 410 761 5118 Chapel Hill Research Group 110 Timberhill Place Chapel Hill, NC 27514 United States of America Ph: +1 919 888 4088, Fax: +1 443 577 4297 Southern Clinical Trials Ltd Forte 2, Level 2, 132 Peterborough Street Christchurch Central, Christchurch 8013 New Zealand Ph: +64 3 337 1979 Canterbury Geriatric Medical Research Trust Burwood Hospital, 300 Burwood Road, Christchurch, 8083, New Zealand Ph: + 64 3 337 7821
Phase of Development	Phase 3
Background and Rationale	Combined administration of acetaminophen and ibuprofen has been shown to provide superior analgesia over administration of comparable doses of either component alone or placebo, when given as an intravenous formulation or as a solid oral tablet in the postoperative setting. This has been demonstrated in three Phase 2/3 clinical trials in patients following third molar removal or arthroscopic knee surgery using oral tablets of Maxigesic® (acetaminophen 500 mg + ibuprofen 150 mg), in one Phase 3 clinical study in dental surgery patients with Combogesic® (acetaminophen 325 mg + ibuprofen 97.5 mg) and in one Phase 3 trial in bunionectomy patients using Maxigesic® IV (acetaminophen 10 mg/ml + ibuprofen 3 mg/ml in 100 ml solution for infusion). The superior efficacy of the combination does not appear to come at the expense of tolerability. In the Phase 3 study of Maxigesic® IV in bunionectomy patients, there were no differences between patients treated with Maxigesic® IV and those treated with intravenous acetaminophen, ibuprofen or placebo in the rate of discontinuations due to adverse events (AEs), the overall incidence of treatment-emergent AEs (TEAEs) or the severity of TEAEs. The incidence of most common TEAEs (affecting ≥ 10% of the study population), including gastrointestinal disorders, nervous system disorders, general disorders and administration site conditions, and skin and subcutaneous tissue disorders was not significantly different between treatment groups. Some differences were observed between

	treatment groups in the incidence of specific AEs, such as vomiting and administration site pain, however these were attributable to the individual components, acetaminophen and ibuprofen respectively. All safety data obtained for Maxigesic® IV to date has come from patients exposed to single doses of the study drug (n=60) or six hourly doses for up to 48 hours (n=75). This study aims to determine the tolerability of repeated doses of Maxigesic® IV over an extended period of exposure.
Objectives	To determine the incidence of treatment-emergent adverse events, and changes in vital signs or clinical laboratory values associated with prolonged exposure to Maxigesic® IV
Study Design	Phase 3, multicenter, open-label, single arm, multiple dose study to evaluate the safety of Maxigesic® IV (acetaminophen 10 mg/ml + ibuprofen 3 mg/ml in 100 ml solution for infusion)
Number of Participants	225 (including 50 participants with at least 5 days exposure)
Main Inclusion Criteria	- Male or female ≥ 18 years of age - Requirement of multiple doses of parenterally administered nonopioid analgesics over multiple days as a result of surgery (non-laparoscopic general, plastic or orthopedic surgery) - Expected stay in facility ≥ 48 hours
Study Drugs & Treatment	Maxigesic® IV (acetaminophen 10 mg/ml + ibuprofen 3 mg/ml in 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 a minimum of 48 hours (8 doses).
Duration of Treatment	The estimated duration of the study for each subject is approximately 42 days, which includes a screening period of up to 30 days, a treatment period of at least 2 days (with up to 50 participants treated for at least 5 days), and a post treatment follow-up visit 7 ± 2 days after the last dose. The first dose is to be administered in the immediate postoperative period, as soon as the patient is stable following surgery.

Study Endpoints	- Incidence of TEAEs at any time during the treatment period
	- The time course of TEAEs
	- Incidence of treatment-related adverse events
	- Incidence of TEAEs of interest:
	  - cardiovascular thrombotic events
	  - gastrointestinal events
	  - renal conditions
	  - hepatic conditions
	  - administration site conditions
	  - bleeding related to surgical procedures
	- Changes in vital sign measurements
	- Changes in clinical laboratory values
	- Patient's global evaluation of study drug

Statistical Methods Summary	All subjects who receive at least one dose of the study drug will be included in the safety population. The safety population will be used for all summaries of study endpoints. Early withdrawals for any reason will be tabulated. The demographic and clinical characteristics of the study population at study entry, including age, gender, race, ethnicity, indication (type of surgery), use

	of concomitant medications (e.g. opioids), vitals and laboratory results will be summarized as means, medians, standard deviations, ranges and frequencies and percentages as appropriate. Treatment-emergent adverse events are defined as events first occurring or worsening during the course of the study, regardless of their relationship to the study drug. Treatment-emergent adverse events will be coded to MedDRA System Organ Class Code and Preferred Term and tabulated as frequencies and percentages in the following time periods: At any timepoint during the observational period; at any timepoint during the treatment period; on Day 1; Day 2; Day 3; Day 4; Day 5; Day 6+; and during follow-up. Clinically significant changes from baseline in vital sign measurements or laboratory test results will be classified as adverse events. The proportion of TEAEs that are considered by the Investigator to be "probably" or "definitely" related to study medication (treatment-related AEs, TRAEs) will be summarized. All cardiovascular, gastrointestinal, renal, hepatic, administration site conditions and bleeding-related AEs will be summarized and the proportion of these that are considered treatment-related will be tabulated. The incidence of TEAEs will be summarized by gender, race, age (<65, 65-75, >75 years), duration of exposure (≤ 48 hours, 48 hours – 4 days, ≥ 5 days) and indication (surgery type). This analysis is subject to recruitment of sufficient participants within each subgroup. Vital sign measurements and clinical laboratory values at each scheduled timepoint will be summarized with standard descriptive statistics, including means, standard deviations and ranges. Summary shift tables will be produced overall and by duration of treatment (≤ 48 hours, 48 hours – 4 days, ≥ 5 days) of the number of cases with normal baseline laboratory tests changed to abnormal at the end of the treatment period, and abnormal baseline laboratory tests worsened at the end of the treatment period, with the severity of changes summarized as proportional effects. The use of concomitant medications following study drug administration will be summarized as frequencies and percentages within ATC-coded drug groups. The frequency and percentage of subjects rating the study drug as 'poor', 'fair', 'good', 'very good' and 'excellent' will be summarized.
Sample Size Calculation	In total, 225 participants will be enrolled in this study, with at least 50 participants exposed to the study drug for at least 5 days. The sample size for this safety study is not based on formal statistical power calculations but will ensure with 95% probability that any TEAEs present in approximately 2% or more of the target population will be identified in this study.

Schedule of Assessments

Schedule of Assessments

Study Assessments	Screening Period (within 30 days before surgery)	Day 1 - ≥5 (Treatment period)				Follow-Up Visit (7 ± 2 days after last dose)
		Day 1 (Prior to Surgery)	Day 1 (Immediately Post Surgery)	Day 2 - ≥5 (Treatment period)	After last dose, prior to discharge	
Informed Consent	✓					
Demographic Data	✓					
Complete Medical History	✓					
Inclusion/Exclusion Criteria	✓	✓				
Physical Examination	✓	✓*			✓	✓
Concomitant Medications	✓	✓	✓	✓	✓	✓
Urine Pregnancy Test[1]	✓	✓*				
Vital Signs (including HR, BP)[2]	✓	✓	✓	✓	✓	✓
ECG[3]		✓		✓	✓	
Urinalysis	✓	✓*			✓	
Biochemistry & Hematology	✓	✓*			✓	
Urine Drug Screening Test	✓	✓*				
Alcohol Breathalyzer Test		✓				
Study Drug Administration[4]			✓	✓		
Global Evaluation of Study Drug					✓	
Adverse Event Monitoring	✓	✓	✓	✓	✓	✓

* Not required if screening done within 7 days of surgery

[1] Females of childbearing potential only

[2] Vital signs will be evaluated at Time 0, prior to and following first dose infusion on Day 1, then each morning prior to the intravenous infusion and after the last dose/prior to discharge/early termination

[3] ECGs will be conducted prior to surgery, at 48 hours after the first dose and after the last dose/prior to discharge

[4] The first dose of the study drug will be administered in the immediate postoperative period, as soon as the patient is stable following surgery

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE(s)	Adverse Event(s)
BP	Blood Pressure
CI	Confidence Interval
CRF(s)	Case Report Form(s)
DBP	Diastolic Blood Pressure
EC	Ethics Committee
ECG	Electrocardiogram
EPP	Evaluable Participant Portion
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GI	Gastrointestinal
hr	Hour(s)
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ITT	Intention to Treat
IUD	Intrauterine Device
kg	Kilogram(s)
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
mmHg	Millimeters of Mercury
NSAID	Non-Steroidal Anti-Inflammatory Drug
NZ	New Zealand
OTC	Over-the-counter
PI	Principal Investigator
PP	Per-protocol Population
SAE(s)	Serious Adverse Event(s)
SAER	Serious Adverse Event Report
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDV	Source Data Verification
SE	Standard Error
sec	Second(s)
TEAE	Treatment-Emergent Adverse Event
TRAE	Treatment-Related Adverse Event
WHO	World Health Organization

1 INTRODUCTION

This protocol describes a Phase 3 safety study designed to examine the safety of a combination of intravenous acetaminophen and ibuprofen (Maxigesic® IV).

1.1 BACKGROUND

Multimodal analgesia with a variety of analgesics (systemic pharmacological therapies with local, regional and neuraxial anesthetics) is strongly recommended for the treatment of postoperative pain (1). In terms of systemic treatments, nonopioid oral or parenteral acetaminophen and/or nonsteroidal anti-inflammatory drugs (NSAIDs) generally form the basis of treatment, in conjunction with opioids of increasing strength as required. Combined treatment with acetaminophen and ibuprofen has been shown to provide superior analgesia over administration of comparable doses of either component alone or placebo, when administered as an intravenous formulation or as a solid oral tablet in the postoperative setting.

AFT Pharmaceuticals Ltd. has sponsored several Phase 2/3 studies which have demonstrated that Maxigesic® tablets (acetaminophen 500 mg + ibuprofen 150 mg, 2 tablets per dose) and Combogesic® tablets (acetaminophen 325 mg + ibuprofen 97.5 mg, 3 tablets per dose) provide superior pain following third molar removal or arthroscopic knee surgery than either drug alone or placebo (2–4).

1.2 DRUG NAME

To extend the therapeutic advantage of Maxigesic®/Combogesic® to patients who may not be able to take oral analgesics, due to patient intubation, sedation, postoperative nausea and vomiting and reduced gastric motility, AFT Pharmaceuticals Ltd. has developed a fixed-dose combination containing acetaminophen 10 mg/ml + ibuprofen 3 mg/ml in 100 ml solution for infusion (Maxigesic® IV). Maxigesic® IV is intended for the relief of mild to moderate pain and the reduction of fever, 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.

1.2.1 Clinical Studies

Maxigesic® IV has been evaluated in two Phase 1 pharmacokinetic studies and one Phase 3 efficacy and safety study.

The first study, AFT-MXIV-01, was a single-dose, open-label, 5-period crossover pharmacokinetic study in 30 healthy volunteers. This study found that pharmacokinetic parameters for acetaminophen and ibuprofen 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 acetaminophen (93.78%) and ibuprofen (96.45%) confirmed the pharmacokinetic equivalence between the oral (Maxigesic®) and intravenous formulations of the fixed dose combination (5).

A second pharmacokinetic study, AFT-MXIV-06, was conducted to compare Maxigesic® IV with brands of

intravenous acetaminophen and ibuprofen that have been approved in the United States, as well as Combogesic® tablets (acetaminophen 325 mg + ibuprofen 97.5 mg, 3 tablets per dose). The study was a single-dose, open-label, 4-period crossover pharmacokinetic study in 30 healthy volunteers. Similar to AFT-MXIV-01, ratios of C_{max}, AUC_t, and $AUC_{0-\infty}$ for Maxigesic® IV to Ofirmev™ and Caldolor™ fell within the 80-125% acceptable bioequivalence range. The relative bioavailability of acetaminophen (83%) and ibuprofen (85%) re-confirmed the pharmacokinetic equivalence between the oral (Combogesic®) and intravenous formulations.

A Phase 3 efficacy and safety study demonstrated the superior analgesic effect of Maxigesic® IV in 276 participants reporting moderate to severe postoperative pain following distal, first metatarsal bunionectomy (6). Patients were treated with six hourly doses of Maxigesic® IV, acetaminophen IV (1000 mg), ibuprofen IV (300 mg) or placebo for 48 hours. The study found that Maxigesic® IV provided superior pain relief to comparable doses of either monocomponent or placebo and reduced the requirement for opioid rescue medication.

Importantly, the superior efficacy of the combination does not appear to come at the expense of tolerability. In the Phase 3 study of Maxigesic® IV in bunionectomy patients, there were no differences between patients treated with Maxigesic® IV and those treated with acetaminophen IV, ibuprofen IV or placebo in the rate of discontinuations due to adverse events (AEs), the overall incidence of treatment-emergent AEs (TEAEs) or the severity of TEAEs. The incidence of most common TEAEs (affecting ≥ 10% of the study population), including gastrointestinal disorders, nervous system disorders, general disorders and administration site conditions, and skin and subcutaneous tissue disorders was not significantly different between treatment groups. Some differences were observed between treatment groups in the incidence of specific AEs, such as vomiting and administration site pain, however these were attributable to the individual components, acetaminophen and ibuprofen respectively.

All safety data obtained for Maxigesic® IV to date has come from patients exposed to single doses of the study drug (n=60) or six hourly doses for up to 48 hours (n=75). The present study aims to determine the tolerability of repeated doses of Maxigesic® IV over an extended period of exposure in a larger population.

1.2.2 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. Previous studies have indicated that there is no change in the safety profile of either drug when administered as a fixed-dose combination. The potential benefit of this study lies in its potential to provide superior analgesia to participants requiring acute pain relief following surgery.

2 TRIAL OBJECTIVES

2.1 STUDY HYPOTHESIS

The study hypothesis is that Maxigesic® IV (intravenous acetaminophen 1000 mg + intravenous ibuprofen 300 mg/ 100 ml solution for infusion) is well tolerated over a treatment period of 5 days, and that the safety profile does not markedly change with extended exposure of 5 days.

2.2 OBEJECTIVES AND ENDPOINTS

2.2.1 Primary Objective and Endpoint

The primary objective is to summarize the safety profile of Maxigesic® IV in patients exposed for ≥ 48 hours.

The primary endpoint is the incidence of treatment-emergent adverse events associated with exposure to Maxigesic® IV.

2.2.2 Secondary Objectives and Endpoints

The following secondary endpoints will be assessed:

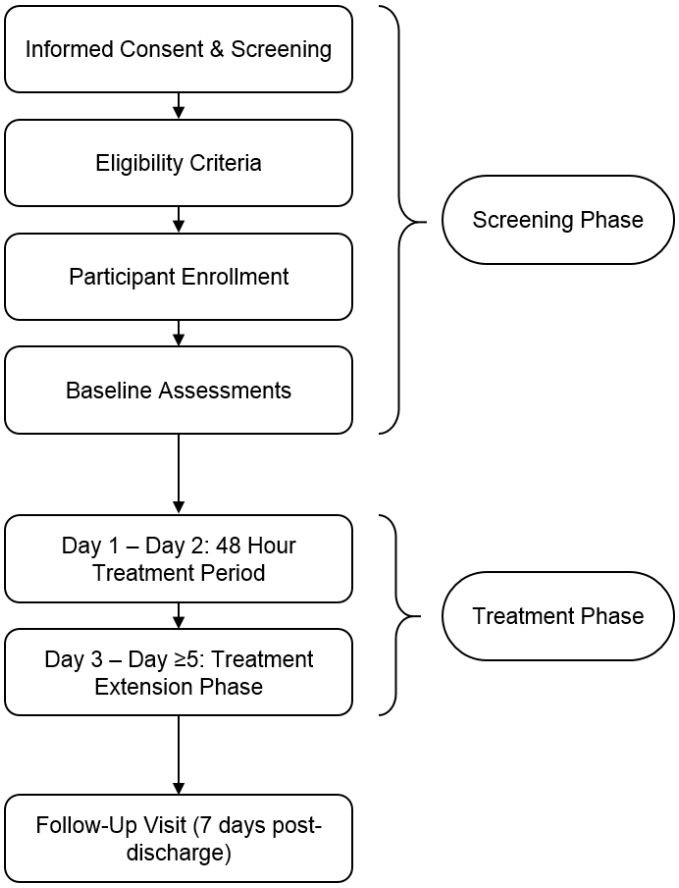
- The time course of treatment-emergent adverse events
- Treatment-related adverse events
- Treatment-emergent adverse events of interest (cardiovascular, gastrointestinal, renal, hepatic, administration site conditions and bleeding-related events)
- Changes in vital sign measurements
- Changes in clinical laboratory values
- Patient's global evaluation of the study drug

3 INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

This study is a Phase 3, multicenter, open-label, single arm, multiple dose study to evaluate the safety of Maxigesic® IV (acetaminophen 10 mg/mL + ibuprofen 3 mg/mL in 100 mL solution for infusion). A flow chart providing a schematic representation of the study design is provided in Figure 1.

Figure 1: Schematic of Trial Design



The study drug, Maxigesic® IV (acetaminophen 10 mg/ml + ibuprofen 3 mg/ml in 100 ml solution for infusion), will be administered by injection into a dedicated indwelling venous cannula, infused over 15 minutes. The study drug will be administered every 6 hours (q6h) for a minimum of 48 hours (8 doses), with some patients treated for at least 5 days (≥ 20 doses).

The study is open-label and single arm. All eligible participants will be assigned to the same study drug, and all patients and study staff will know the treatment being administered.

3.2 DISCUSSION OF STUDY DESIGN

The study is designed to investigate the safety and tolerability of Maxigesic® IV in a larger study population over an extended period of time. As Maxigesic® IV may be used for longer than 48 hours in clinical practice, the study aims to determine if prolonged exposure to Maxigesic® IV results in any changes to the safety profile.

The study is designed as a descriptive investigation of the safety profile of Maxigesic® IV in a larger sample size than has previously been evaluated. The study aims is to determine the safety profile and the temporal nature of the safety profile after extended exposure to Maxigesic® IV for ≥ 48 hours.

4 PATIENT POPULATION

4.1 NUMBER OF PATIENTS

In total, 225 participants who meet all the eligibility criteria will be enrolled into the study, including at least 50 participants with an anticipated period of exposure of ≥ 5 days. The gender distribution of enrolled patients should be approximately evenly divided amongst males and females, with no more than 60% of participants being of either gender.

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 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. Requires multiple doses of parenterally administered nonopioid analgesics over multiple days as a result of surgery (non-laparoscopic general, plastic or orthopedic surgery).
4. Has an expected stay in facility ≥ 48 hours.
5. Has a body weight ≥ 45 kg.
6. If female and of childbearing potential, is nonlactating and nonpregnant (has negative urine pregnancy test results at Screening and on the day of surgery prior to surgery, if greater than 7 days between Screening and surgery).
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:
    i) 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.
    ii) Total abstinence from sexual intercourse since the last menses before study drug administration through completion of final study visit.
    iii) Intrauterine device (IUD).
    iv) 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 remain at the study site for at least 48 hours and to attend a follow-up visit at 7 ± 2

days after the last dose of study drug.

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 participates in the study or could confound the results of the study.
3. Has a 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 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.
6. Has tested positive either on the urine drug screen or on the alcohol breathalyzer test. Subjects who test positive and can produce a prescription for the medication from their physician may be considered for study enrolment at the discretion of the Investigator.
7. 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.
8. 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.
9. Is considered by the Investigator, for any reason to be an unsuitable candidate to receive the study drug.
10. 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).
11. Is currently receiving anticoagulants (e.g. heparin or warfarin).
12. 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).
13. 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.

14. 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).
15. Has any clinically significant laboratory finding at screening that, in the opinion of the Investigator, contraindicates study participation.
16. 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.

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 from those participants who specifically withdraw consent to release of such information.

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

Maxigesic® IV: acetaminophen 10 mg/ml + ibuprofen 3 mg/ml in 100 ml solution for infusion.

The first dose of the study drug is to be administered in the immediate postoperative period, as soon as the patient is stable following surgery.

The study drug will be administered by injection into a dedicated indwelling venous cannula, infused over 15 minutes. The study drug will be administered every 6 hours (q6h) for a minimum of 48 hours up to at least 5 days, with a maximum of 4 doses within a 24 hour period. The maximum duration of exposure will be at the discretion of the Investigator.

5.2 IDENTITY OF INVESTIGATIONAL PRODUCTS

The active ingredients of Maxigesic® IV are acetaminophen and ibuprofen. AFT Pharmaceuticals will supply the study drug. The study drug is manufactured by S.M. Farmaceutici S.R.L. located in Zona Industriale-85050 TITO (PZ) Italy, at their GMP approved manufacturing facility. The study drug is provided as a sterile solution in 100 ml glass vials closed with a stopper and sealed with aluminum caps. Maxigesic® IV has been shown to be stable for 24 months when stored at 25°C (77°F).

The study drug supplied for use in 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 patient not participating in this study.

The Investigator or pharmacy designee will maintain an inventory record of study drug dispensed to assure regulatory authorities and the Sponsor that the investigational new drug has not been dispensed to any person who is not a participant under the terms and conditions set forth in this protocol. At the termination of the study, all unused study drug (once it has been inventoried and the monitor has reviewed the accountability records and any retesting procedures completed) will be destroyed, and a destruction certificate will be issued by a licensed destruction company.

5.3 RANDOMIZATION

As the study is designed as a single arm study, no randomization will occur. All participants who meet the eligibility criteria will be enrolled and administered the study drug.

5.4 BLINDING

The study is open-label; all patients and study staff will know the treatment being administered.

5.5 PROHIBITED CONCOMITANT MEDICATIONS

The following concomitant medications are prohibited during the study period:

1. Any medication containing acetaminophen
2. Any nonsteroidal anti-inflammatory drugs, including ibuprofen
3. Any other medications which might, in the Investigators' opinion, pose a potential threat to patient safety

At the discretion of the Investigator, opioids are permitted to be used as supplementary analgesia if pain is not sufficiently controlled by the investigational product. The use of any supplementary analgesia shall be documented in the Case Report Form.

5.6 TREATMENT COMPLIANCE

Compliance will be assessed by recording the volume and timing of each dose administered in the Case Report Form (CRF). All participants who receive at least one dose of the study drug will be included in the analysis.

6 EFFICACY, PHARMACOKINETIC AND SAFETY VARIABLES

6.1 EFFICACY AND SAFETY MEASURES ASSESSED

6.1.1 Safety Variables

The safety variables to be recorded are treatment-emergent adverse events (TEAEs), vital signs, ECGs, and clinical laboratory values.

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.

Participants will complete a global evaluation of the study drug (Appendix 3) at the end of the treatment period or upon early withdrawal from the study, before discharge from the study site.

7 SEQUENCE OF PROCEDURES

An overview of the sequence of procedures and study assessments is summarized in Table 1.

Table 1: Schedule of Assessments

Study Assessments	Screening Period (within 30 days before surgery)	Day 1 - ≥5 (Treatment period)				Follow-Up Visit (7 ± 2 days after last dose)
		Day 1 (Prior to Surgery)	Day 1 (Immediately Post Surgery)	Day 2 - ≥5 (Treatment period)	After last dose, prior to discharge	
Informed Consent	✓					
Demographic Data	✓					
Complete Medical History	✓					
Inclusion/Exclusion Criteria	✓	✓				
Physical Examination	✓	✓*			✓	✓
Concomitant Medications	✓	✓	✓	✓	✓	✓
Urine Pregnancy Test[1]	✓	✓*				
Vital Signs (including HR, BP)[2]	✓	✓	✓	✓	✓	✓
ECG[3]		✓		✓	✓	
Urinalysis	✓	✓*			✓	
Biochemistry & Hematology	✓	✓*			✓	
Urine Drug Screening Test	✓	✓*				
Alcohol Breathalyzer Test		✓				
Study Drug Administration[4]			✓	✓		
Global Evaluation of Study Drug					✓	
Adverse Event Monitoring	✓	✓	✓	✓	✓	✓

* Not required if screening done within 7 days of surgery

[1] Females of childbearing potential only

[2] Vital signs will be evaluated at Time 0, prior to and following first dose infusion on Day 1, then each morning prior to the intravenous infusion and at discharge, early termination

[3] ECGs will be conducted prior to surgery, at 48 hours after the first dose and after the last dose/prior to discharge

[4] The first dose of the study drug will be administered in the immediate postoperative period, as soon as the patient is stable following surgery

7.1 PRETREATMENT PERIOD

Screening will occur up to 30 days prior to the day of surgery (Day 1). 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, hematological, neurological, musculoskeletal or psychiatric conditions (if any), allergy to food or drugs and medication history for the previous three months.
- Physical examination including an assessment of vital signs (heart rate, blood pressure, temperature, respiratory rate)
- Recording of concomitant medications
- Urine pregnancy tests (females of childbearing potential only)
- Urine analysis
- Urine drug screening test (amphetamines, barbiturates, benzodiazepines, cocaine, methamphetamines, opiates, phencyclidine (PCP), and tetrahydrocannabinol (THC))
- Blood screening tests including:
    - Hematology:
        - Hemoglobin
        - Hematocrit
        - 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

If screening is conducted more than 7 days prior to surgery, the following evaluations will be performed on Day 1, prior to surgery:

- Physical examination
- Urine pregnancy tests (females of childbearing potential only)
- Urine analysis
- Blood screening tests as described above
- Urine drug screening test as described above

The following evaluations will be performed on Day 1 prior to surgery, regardless of whether screening was conducted within 7 days of the surgery:

- Recording of concomitant medications
- Assessments of vital signs (heart rate, blood pressure, temperature, respiratory rate)
- Electrocardiogram
- Alcohol breathalyzer test

Adverse events and concomitant medications will be recorded from the time of enrollment.

7.2 TREATMENT PERIOD

The first dose is to be administered in the immediate postoperative period, as soon as the patient is stable following surgery.

The treatment period will commence at the start of administration of the first dose of study drug administration and will conclude at the clinician's discretion. The minimum exposure is anticipated to be 48 hours (8 doses), with at least 50 patients treated for at least 5 days (≥ 20 doses). Assessments to be conducted at the end of the treatment period should be done after the last dose (if possible, approximately 6 hours after the last dose) and prior to discharge.

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

- Patient's global evaluation of study drug at the end of the treatment period or at early withdrawal

In addition, the following evaluations will be completed:

- Vital signs will be evaluated before and following the first dose infusion on Day 1, then each morning prior to the intravenous infusion and at the end of the treatment period or early withdrawal
- Electrocardiogram at 48 hours after the first dose and at the end of the treatment period
- A physical examination will be conducted at the end of the treatment period or at early withdrawal
- Blood tests as described above will be conducted at the end of the treatment period or at early withdrawal
- Urine analysis will be conducted at the end of the treatment period or at early withdrawal

Adverse events and concomitant medications will be recorded throughout the treatment period. All doses of the study drug will be recorded, including volume and timing.

7.3 FOLLOW-UP

A follow-up visit will be conducted 7 ± 2 days after the last dose of study drug. At this follow-up, any additional adverse event and concomitant medication data will be collected. Additionally, a physical examination including an assessment of vital signs (heart rate, blood pressure, temperature, respiratory rate) will be conducted.

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, unfavorable 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., hematological, biochemical, hormonal) or other clinical tests (e.g., ECG), whether or not considered treatment related.

Treatment-emergent adverse events (TEAEs) are defined as events that emerge during treatment, having been absent pre-treatment, or that worsen relative to the pre-treatment status (ICH E9).

Treatment-emergent adverse events that are considered by the Investigator to be "probably" or "definitely" are treatment-related adverse events (TRAEs).

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 enrolled in the 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 jeopardize 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 ADVERSE EVENT REPORTING PERIOD

Adverse event data will be collected from the time of enrollment through to the follow-up visit, 7 ± 2 days after administration of the last dose.

8.3 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.

8.4 PROCEDURE FOR SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR

8.4.1 Reporting to the Sponsor

In addition to entering each serious adverse event irrespective of causality on the appropriate page of the 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 (+64 9 488 0234) within 24 hours from the point in time when the SAE is realized. 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 regarding 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 after the study period that he or she determines to be causally related to study medication, the event should also be reported through this process.

8.4.2 Reporting to Local Ethics Committee/Institutional Review Board

All adverse drug reactions (ADRs) reporting shall be compliant to applicable local IRB/IEC requirements. 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.

8.4.3 Reporting to Regulatory Agencies

8.4.3.1 Fatal or Life-Threatening Unexpected Adverse Drug Reactions

An ADR is considered "fatal or life threatening" if, in the review of either the Investigator or Sponsor, its occurrence places the participants at immediate risk of death. It does not include an adverse event or adverse drug reaction that, had it occurred in a more severe form, might have caused death.

Fatal or life-threatening, unexpected ADRs occurring in clinical investigations is subject to expedited reporting. Regulatory agencies should be notified (e.g., by telephone, facsimile transmission, or in writing) as soon as possible but no later than 7 calendar days after first knowledge by the Sponsor that a case qualifies, followed by as complete a report as possible within 8 additional calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products (CPMP/ICH/377/95).

8.4.3.2 All Other Serious, Unexpected Adverse Drug Reactions

Serious, unexpected ADRs that are not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days after first knowledge by the Sponsor that the case meets the minimum criteria for expedited reporting (CPMP/ICH/377/95).

It is recommended to use the CIOMS form, which contains the information as listed in the attachment 1 of ICH E2A Clinical Safety Data Management Guideline.

Adverse events which are not subject to expedited reporting shall be summarized in a periodic safety reporting according to applicable local regulatory requirements (e.g. Medsafe 6 month's progress report / US FDA IND annual report).

8.5 THE DATA SAFETY MONITORING BOARD

No Data Safety Monitoring Board reviews are planned for this study.

9 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 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.

10 STATISTICAL PLAN

This is a Phase 3, multicenter, open-label, single arm, multiple dose study to evaluate the safety of Maxigesic® IV. As a single arm study, the study is descriptive in nature, however summaries of safety endpoints will be generated within specific time intervals and by pre-specified subgroups.

10.1 SAMPLE SIZE

In total, 225 participants will be enrolled in this study, with at least 50 participants exposed to the study drug for at least 5 days. The sample size for this safety study is not based on formal statistical power calculations but will ensure with 95% probability that any TEAEs present in approximately 2% or more of the target population will be identified in this study.

10.2 DEFINITIONS

10.2.1 Patient Population

The safety analysis will be on all participants who are administered at least one dose of study medication with treatment allocation for analysis based on the actual treatment the participant received.

10.2.2 Observational Period

The observational period is from administration of the first dose of the study drug to the follow-up visit, 7 ± 2 days after administration of the last dose. The treatment period is from administration of the first dose of the study drug to approximately 6 hours after the last dose, and prior to discharge.

10.3 STATISTICAL ANALYSES

10.3.1 Demographic and Baseline Characteristics

The demographic and baseline clinical characteristics of the study population including age, gender, race, ethnicity, indication (type of surgery), vitals, laboratory values and concomitant medications, will be summarized as means, medians, standard deviations, ranges and frequencies and percentages as appropriate.

10.3.2 Treatment Compliance

Participants whose study drug usage, or dose rate exceeds the limitations provided by the study protocol will be included in a list of protocol deviations. The potential effect of such deviations on the resulting clinical evaluations will be discussed in the study report.

10.3.3 Exposure

To evaluate the extent of drug exposure during the trial, tabular summaries of study drug usage (number of doses, duration of exposure, mean interval between doses) will be presented. Early withdrawals for any reason will be tabulated.

10.3.4 Primary Analyses

The primary endpoint is the incidence of TEAEs associated with exposure to Maxigesic® IV. TEAEs occurring at any timepoint during the treatment period will be coded to MedDRA System Organ Class Code and Preferred Term and tabulated as frequencies and percentages.

10.3.5 Secondary Analyses

10.3.5.1 Time Course of Treatment-Emergent Adverse Events

TEAEs will be tabulated as frequencies and percentages during the following time periods:

- At any time during the observational period
- On each day during the treatment period:
    - Day 1
    - Day 2
    - Day 3
    - Day 4
    - Day 5
    - Day 6+
- During follow-up

Days will be defined as 24-hour intervals after the first dose of study drug.

10.3.5.2 Treatment-Related Adverse Events

TEAEs considered by the investigator to be “probably” or “definitely” are treatment-related AEs; TRAEs. TRAEs will be summarized in the same manner as TEAEs.

10.3.5.3 Treatment-Emergent Adverse Events of Interest

All cardiovascular, gastrointestinal, renal, hepatic, administration site conditions and bleeding-related TEAEs will be summarized as frequencies and percentages, and the proportion of these that are considered treatment-related will be tabulated.

10.3.5.4 Changes in Vital Signs

Clinically significant changes from baseline in vital sign measurements will be classified as adverse events

and included in all analyses of adverse events.

Vital sign measurements at each scheduled timepoint will be summarized with standard descriptive statistics.

10.3.5.5 Changes in Clinical Laboratory Values

Clinically significant changes from baseline in laboratory test results will be classified as adverse events and included in all analyses of adverse events.

Clinical laboratory values at each scheduled timepoint will be summarized with standard descriptive statistics. Summary shift tables will be produced overall and by duration of treatment (≤ 48 hours, 48 hours – 4 days, ≥ 5 days), of the number of cases with normal baseline laboratory tests changed to abnormal at the end of the treatment period, and abnormal baseline laboratory tests worsened at the end of the treatment period, with the severity of changes summarized as proportional effects.

10.3.5.6 Patient's Global Evaluation of the Study Drug

The patient's global evaluation of the study drug will be summarized by the number and percentage of subjects within each category.

10.3.6 Subgroup Analyses

The incidence of TEAEs will be summarized within the following subgroups as sample sizes permit:

- gender
- race
- age (patients aged <65 years, 65-75 years, >75 years)
- duration of exposure (dosed for ≤ 48 hours, dosed for 48 hours – 4 days, dosed for ≥ 5 days)
- indication (type of surgery)

Subgroup analyses are subject to recruitment of sufficient participants in each group.

10.3.7 Other Safety Analyses

10.3.7.1 Severity and Relationship of Treatment Emergent Adverse Events to the Study Drug

In addition to the primary and secondary analyses of the incidence of TEAEs, TEAEs occurring at any timepoint during the treatment period will be coded to MedDRA System Organ Class Code and Preferred Term and tabulated as frequencies and percentages by severity class and relationship to the study drug.

10.3.7.2 Concomitant medication

The use of concomitant medications following study drug administration will be summarized as frequencies and percentages within ATC-coded drug groups.

10.3.7.3 Electrocardiograms

Clinically significant changes from baseline in ECG results will be classified as adverse events and included in all analyses of adverse events.

Summary shift tables will be produced overall and by duration of treatment (≤ 48 hours, 48 hours – 4 days, ≥

5 days), of the number of cases with normal baseline ECGs changed to abnormal at 48 hours and/or the end of the treatment period, and abnormal baseline ECGs worsened at 48 hours and/or the end of the treatment period.

10.4 MISSING DATA

As the study is focused on safety and tolerability, and is conducted within the trial clinics, it is expected that all adverse event data will be collected, even if some participants withdraw from the study medication.

10.5 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.

10.6 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.

11 RECORDS RETENTION

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 nor 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.

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 center(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 center(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 THE 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, authorized regulatory officials, 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 authorized 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 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 randomized 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 local EC and ICH GCP requirements. I further agree to report to the Sponsor any adverse experiences in accordance with the terms of this protocol, local regulatory (Medsafe) requirements and FDA regulation, 21 CFR 312.64.

_____	_____	_____
Principal Investigator's Name (printed)	Signature	Date

16 REFERENCE LIST

1. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016 Feb;17(2):131–57.

2. Merry AF, Gibbs RD, Edwards J, Ting GS, Frampton C, Davies E, et al. Combined acetaminophen and ibuprofen for pain relief after oral surgery in adults: a randomized controlled trial. Br J Anaesth. 2010 Jan 1;104(1):80–8.

3. Atkinson HC, Currie J, Moodie J, Carson S, Evans S, Worthington JP, et al. Combination paracetamol and ibuprofen for pain relief after oral surgery: a dose ranging study. Eur J Clin Pharmacol. 2015 May;71(5):579–87.

4. Daniels SE, Atkinson HC, Stanescu I, Frampton C. Analgesic Efficacy of an Acetaminophen/Ibuprofen Fixed-dose Combination in Moderate to Severe Postoperative Dental Pain: A Randomized, Double-blind, Parallel-group, Placebo-controlled Trial. Clin Ther. 2018 Oct;40(10):1765-1776.e5.

5. Atkinson HC, Stanescu I, Frampton C, Salem II, Beasley CPH, Robson R. Pharmacokinetics and Bioavailability of a Fixed-Dose Combination of Ibuprofen and Paracetamol after Intravenous and Oral Administration. Clin Drug Investig. 2015 Oct;35(10):625–32.

6. AFT Pharmaceuticals Ltd. 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. 2018 May. Report No.: CSR/MXIV-07/03.

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 edema 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.

Hematological Monitoring:
Blood dyscrasias have been rarely reported. Participants on long-term therapy with ibuprofen should have regular hematological 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 hemostatic 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: PATIENT'S GLOBAL EVALUATION OF THE 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 the treatment period/early withdrawal.