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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Statistical Analysis Plan

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Approval Form

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1 TITLE

A Phase 3, Randomized, Double-Blind, Multiple-Dose, Parallel-Group and Placebo controlled Study of Maxigesic® IV, IV Acetaminophen, and IV Ibuprofen for the treatment of acute postoperative pain after bunionectomy.

2 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.

3 STUDY DESIGN AND OBJECTIVES

3.1 Design

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.

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 Day 7 (±2 days).

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 anaesthesia. The regional anaesthetic technique to be used for this surgery comprises a combination of a PSB to establish and maintain surgical field anaesthesia (local anaesthesia using a Mayo block with a short acting anaesthetic will be allowed to augment surgical field anaesthesia 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. Subjects will receive midazolam and/or propofol for initial sedation at the anaesthesiologist's discretion. After adequate sedation is achieved, the anaesthesiologist will inject approximately 5 mL lidocaine 1% (plain) (or suitable short acting local anaesthetic 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 anaesthesiologist 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 anaesthesia. If the PSB is not sufficient to provide adequate surgical anaesthesia, a standard Mayo block (local anaesthesia) may be established using lidocaine 2% (plain) not to exceed 25 mL. The time, date, dose, and route of all local anaesthetics will be recorded in the CRF.

The regional anaesthesia will be established using a popliteal sciatic nerve block (PSB) after which subjects will undergo primary, unilateral, first metatarsal bunionectomy under regional anaesthesia. The regional anaesthesia will be continued postoperatively via a continuous anaesthetic 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 anaesthetic infusion fails to provide adequate anaesthesia.

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 anaesthetic 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 anaesthetic 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).

During the 9-hour qualification period after discontinuation of the anaesthetic 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 anaesthesia, subjects will not be eligible for enrolment 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:

- Maxigesic® IV (acetaminophen 10 mg/1 mL + ibuprofen 3 mg/mL solution for infusion)
- Acetaminophen IV (acetaminophen 10 mg/1 mL solution for infusion)
- Ibuprofen IV (ibuprofen 3 mg/mL solution for infusion)
- Placebo solution for infusion

During the treatment period (Day 1-3) study drugs will be administered q6h for a total of 8 doses over 48 hours, and the following participant reported measurements will be made:

- 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 and 2 hours after each subsequent dose (doses 2-8) of the study drug 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 and 2 hours after each subsequent dose (doses 2-8) of the study drug 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
- Time to onset of perceptible and meaningful pain relief after the first study drug administration, using the two-stopwatch method during the first dosing period
- Patient's global evaluation of study drug at the end of the 48 hours treatment period

Patients will be discharged on Day 3 after 48 hours and a final follow-up phone call will be conducted on Day 7 (±2 days).

3.2 Efficacy Objective

To determine the efficacy of Maxigesic® IV, acetaminophen IV, ibuprofen IV and placebo IV for the treatment of acute postoperative pain after bunionectomy.

The Efficacy Objective of this study will be addressed by analysis on the following efficacy endpoints.

Primary Efficacy Endpoint

- Time-adjusted Summed Pain Intensity Difference (SPID) from baseline over 48 hours (Time-adjusted $SPID_{48}$)

Secondary Efficacy Endpoints

- Time-adjusted Summed Pain Intensity Difference (SPID) from baseline over 6, 12 and 24 hours (Time-adjusted $SPID_6$, Time-adjusted $SPID_{12}$, and Time-adjusted $SPID_{24}$, respectively)
- Total Pain Relief (TOTPAR) over 6, 12, 24 and 48 hours after the first dose of study drug ($TOTPAR_6$, $TOTPAR_{12}$, $TOTPAR_{24}$, and $TOTPAR_{48}$, respectively)
- VAS Pain intensity scores (mm) at each scheduled assessment time point after the first dose of study drug
- Pain Intensity Difference (PID) at each scheduled VAS assessment time point after the first dose of study drug
- Pain Relief Score at each scheduled assessment time point after the first dose of study drug
- Peak Pain Relief
- Time to Peak Pain Relief
- Response Rate
- Time to Response
- Time to onset of analgesia (perceptible and meaningful pain relief using two stopwatch method)

- Time to first use of rescue medication
- Proportion of patients using rescue medication
- Total use of rescue medication over 24 and 48 hours after first dose of study drug
- Patients' global evaluation of study drug

3.3 Safety Objective

To determine the incidence of treatment-emergent adverse events (AEs) and changes in vital sign measurements.

4 GENERAL ANALYSIS DEFINITIONS

4.1 Treatment Allocation

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 anaesthetic block.

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.

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

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 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.

4.2 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 [SE=0.6] in mean time-adjusted SPID between Maxigesic® IV and each of the three comparator study groups.

4.3 Participant Populations

4.3.1 *Intention-to-treat (ITT) Population*

The Intent-To-Treat (ITT) population 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.

4.3.2 *Per Protocol (PP) Population*

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. Additional Analyses of efficacy measures using the Per Protocol (PP) population may be performed as a sensitivity analysis of the above ITT analyses if the PP population is <90% of the ITT population.

4.3.3 *Safety Population*

The safety population is the population for all safety assessments. 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.

4.4 Observational Period

The observational period for the study will be from the first dose of study medicine (post-operatively) up to 48 hours after the first dose.

For safety data, adverse events will be assessed following participant's randomization during the hospital stay, and during a follow-up phone call on Day 7 (±2 days).

5 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, gender, race, weight, height, BMI, medical history, surgery duration, and baseline vitals and 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.

These data will be examined for any profound imbalances between randomised treatments, and these imbalances reported. If potentially confounding influences are thus identified, appropriate statistical means will be used to mitigate these, and they will be reported and discussed in any reports or publications arising from the study. No formal hypothesis testing will be conducted on these baseline variables.

6 PARTICIPANT DISPOSITION

A flowchart will be produced showing the flow of participants throughout the study. The numbers of participants consented, screened, randomized, dosed and completed the study will be summarized.

The time intervals between consent & randomisation and randomisation & the start of study drug administration will be summarised for each randomised group. Any participants who were randomised but did not receive at least one dose of study medication will be individually listed with explanation, by randomised group.

Any patients inappropriately randomised (e.g. subsequent to randomisation are found to violate inclusion/exclusion criteria) will also be individually listed with their inclusion or exclusion violations. Participants who use prohibited concomitant medications during the study will be individually listed with the study medication, dosage, start and finish dates.

Total participant numbers for the ITT and PP populations will be summarised by randomised group and total participant numbers in the Safety Population will be summarised by treatment actually received (should be in accordance with randomized allocation).

7 STUDY MEDICATION AND CONCOMITANT THERAPY

7.1 Compliance

To evaluate the degree of treatment compliance during the trial, tabular summaries of study drug usage per 24 hour interval will be presented for each randomised group.

Participants whose study drug usage, or dose rate exceeded 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.

7.2 Concomitant Medications

Concomitant medications commenced during the study will be coded and summarised as frequencies and percentages by randomised group. The timing of the start of these new medications relative to the start of study medication will also be summarised. Medications will be grouped into drug classes for these summarises.

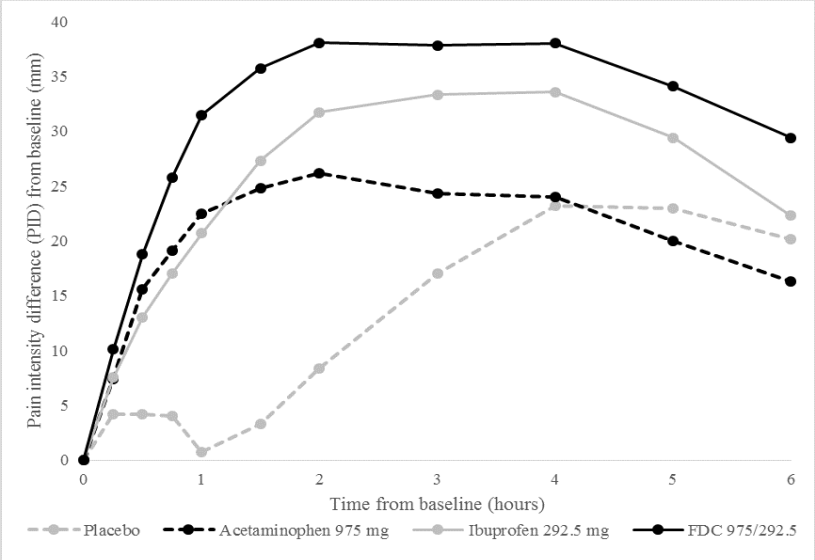
8 EFFICACY ANALYSES

8.1 Primary Efficacy Analysis

The primary efficacy endpoint is the time-adjusted Sum of Pain Intensity Differences over 48 hours after the first dose of study medication (time-adjusted $SPID_{48}$).

A Pain Intensity Difference is the difference between the Visual Analogue Scale (VAS) pain score recorded at baseline and a score recorded at any time after the first dose of study medication. Taken together, a patient's PID scores capture the pain relief profile attributable to the assigned study medication (an example from 6 hours' worth of data from study AFT-MX-6 is presented in Figure 1). The extent of pain relief can then be calculated by the Area Under the Curve the PID scores (also referred to as the Sum of Pain Intensity Differences [SPID]).

Figure 1: Example PID curves obtained from AFT-MX-6 for the first 6 hours after baseline. FDC 975/292.5 = 3 tablets of a Fixed Dose Combination of Acetaminophen 325 mg & ibuprofen 97.5 mg



For the calculation of the SPID, intermittent missing VAS scores will be imputed by linear interpolation of adjacent values immediately preceding and following the missing value. Additionally, in the event that a patient required rescue medication, the SPID will be calculated up until the first Pre-Rescue VAS pain assessment (inclusive):

1. Example 1: Patient X recorded VAS pain up until 48 hours, but consumed their first dose of rescue medication 2.5 hours after the first dose of study medication. The Time-adjusted SPID will be calculated using the scheduled and pre-rescue VAS pain intensity assessments made up to 2.5 hours after the first dose.
2. Example 2: Patient Y recorded VAS pain intensity scores up until 44 hours after the first dose of study medication and did not require any rescue medication. The Time-adjusted SPID will be calculated using the scheduled VAS pain intensity assessments made over 44 hours.

Subsequently, $SPID_{48}$ scores will be adjusted by the time interval from baseline to the final VAS score used in the SPID, using the following formula:

Time-adjusted $SPID_{48}$ (mm) = SPID (mm*hr) / Time (hr)

The analysis of Time-adjusted $SPID_{48}$ will be performed on the Intention to Treat (ITT) population 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 Maxigesic® IV with each of the three comparators using a sequential testing strategy to preserve the two-sided type I error rate at $\alpha=0.05$. 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 Maxigesic® IV will be conducted in the following sequence: 1. Placebo IV, 2. Acetaminophen IV, and 3. Ibuprofen IV.

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.

The primary efficacy variable will also be summarized by site, with no formal statistical comparisons between sites.

8.2 Secondary Efficacy Analyses

Continuous Secondary Efficacy Endpoints will be summarized by treatment group using means, standard errors, medians, minima and maxima. These endpoints will be analysed using ANCOVA model with the baseline pain intensity as a covariate and these results summarized as the mean differences between treatments with 95% CIs. Continuous Secondary Efficacy Endpoints include the following:

- Time-adjusted $SPID_6$
- Time-adjusted $SPID_{12}$
- Time-adjusted $SPID_{24}$
- VAS pain intensity score (mm) at each scheduled time point
- PID (mm) at each scheduled time point
- Total Pain Relief over 6 hours ($TOTPAR_6$)
- $TOTPAR_{12}$
- $TOTPAR_{24}$
- $TOTPAR_{48}$

Time-adjusted $SPID_6$ through to $SPID_{24}$ will be derived in a similar manner to the Time-adjusted $SPID_{48}$ (i.e. up until the first Pre-Rescue VAS inclusive).

Total Pain Relief (TOTPAR) is a measure of total Area Under the Curve of Pain Relief scores, weighted by time. For all TOTPARs, in the event that a patient required rescue medication (either IR oxycodone 5-10 mg or morphine 2-4 mg), the Area Under the Pain Relief curve will be calculated up until the first Pre-Rescue Pain Relief score (inclusive).

The Ordinal Secondary Efficacy Endpoints 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. Ordinal Secondary Efficacy Endpoints include the following:

- Pain Relief score at each scheduled time point
- Peak Pain Relief
- Total Dose (mg) of primary (oxycodone) and secondary (morphine) rescue medication over first 24 hours and the full 48 hour study period
- Total oral Morphine Milligram Equivalent (MME) dose of all rescue medication over the first 24 hours and the full 48 hour study period
- Global Evaluation of Study Drug

A patient's Peak Pain Relief will be determined from all pain relief ratings recorded prior to the first dose of rescue medication (if taken), or up until the end of participation in the double-blind treatment period (if no rescue taken).

The oral Morphine Milligram Equivalent (MME) of PO oxycodone is obtained by multiplying the dose of Oxycodone by 1.5 (1). The oral MME of IV morphine is obtained by multiplying the dose of IV morphine by 3.0 (2). The MME is a useful tool for comparing to doses with other oral opioid drugs such as hydrocodone, hydromorphone, oxymorphone, fentanyl, and codeine, etc.

Time to Event Secondary Efficacy Endpoints will be summarized for each treatment group using the Kaplan-Meier Method. For these time-to-event analyses any participants who do not experience the event, will be censored at the end of the relevant observation period. 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.

Time to onset of analgesia (measured as time to perceptible pain relief and 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.

Log-rank tests will also be used to compare the Maxigesic IV group with each of the comparators for the time-to-event outcomes. Time to Event Secondary Efficacy Endpoints include the following:

- Time to Perceptible and Meaningful Pain Relief (Two Stopwatch Assessment)
- Time to Peak Pain Relief
- Time to Response
- Time to first dose of Rescue Medication

The Response Rate, defined as the percentage of patients that obtain at least a 50% reduction in baseline VAS pain, will be analysed using a Chi-square test. An individual patient's response to treatment will be determined from their VAS scores recorded prior to the first dose of rescue medication (if taken), or up until the end of their participation in the double-blind treatment period (if no rescue taken).

Additionally, 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® IV with the three comparator groups.

All secondary endpoints will be analysed using all participants in the ITT population that have the appropriate assessment of the endpoint or an estimate. There will be no correction for multiple comparisons for the analyses of the secondary endpoints. A two-tailed p-value <0.05 will be taken to indicate statistical significance for all analyses of secondary efficacy endpoints.

8.3 Additional analyses

8.3.1 Subgroup Analyses

Analysis of the primary efficacy endpoint will also be presented by gender, age, ethnicity and baseline severity subgroups. A consistency of treatment effect among subgroups will be tested for each of the subgroups.

Secondary analyses may explore the consistency of treatment effects across gender, ethnicity and baseline severity subgroups. These factors would be included as covariates in the analyses and the interaction between the sub-group factor and randomised treatment would be tested.

8.3.2 Sensitivity Analyses

Additional Analyses of efficacy measures using the Per Protocol (PP) population may be performed as a sensitivity analysis of the above ITT analyses if the PP population is <90% of the ITT population.

Sensitivity analyses will be undertaken on the Primary Efficacy endpoint (Time-adjusted $SPID_{48}$) for the ITT population to determine the impact of calculating the Time-adjusted $SPID_{48}$ using all VAS pain assessments recorded up until the first Pre-Rescue VAS (inclusive. This will include the following approaches:

1. Calculate the Time-adjusted $SPID_{48}$ using all VAS pain assessments recorded up until the first Pre-Rescue VAS score (inclusive), and by carrying forward the first Pre-Rescue VAS score until the end of participation in the study
2. Calculate the Time-adjusted $SPID_{48}$ using the full complement of VAS pain assessments (includes both Scheduled AND Pre-Rescue VAS scores recorded by each patient).
3. Calculate the Time-adjusted $SPID_{48}$ by carrying forward the Pre-Rescue VAS score up to 4 hours after each rescue treatment. 4 hours is consistent with the duration of action of both rescue medications (oxycodone and morphine). In the event that a patient requires two or more doses of rescue medication within a 4 hour interval, a subsequent Pre-Rescue VAS score will override the previous one (i.e. Pre-Rescue VAS scores will not supplant subsequent Pre-Rescue VAS scores).

Additionally, sensitivity analyses will be undertaken on all pain intensity and pain relief outcomes where multiple imputation was used for early withdrawals (see Section 11 Missing Data). Theses analyses will only include the recorded data (i.e. no imputation) and the outcome will be used to show the sensitivity of the main results to the imputation process.

Statistical significance is not required from all these sensitivity analyses but the analyses will be presented and inconsistencies with the primary efficacy endpoint analysis will be discussed.

9 SAFETY ANALYSES

Safety analyses will be performed using the safety population, defined as all subjects who are treated with study drug (ITT) with group allocation according to the treatment they actually received. Treatment-emergent Adverse events coded to MedDRA v 20.0 Preferred Term and System Organ Class Code will be tabulated as frequencies and percentages by treatment group, and by treatment group and severity class and treatment group and relatedness to study drug. 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.

The frequencies and proportions of participants discontinuing as a result of adverse events will also be listed and summarised. Serious adverse events will be individually listed by randomised group.

Changes in vital signs from baseline at the following points will compared between treatment groups:

- End of Infusion of first dose
- Prior to 5th Dose of study drug
- At discharge on Day 3/early termination

10 PROTOCOL VIOLATIONS

All protocol violations and deviations will be individually listed by randomised group.

11 MISSING DATA

Intermittent missing VAS scores will be imputed by linear interpolation of adjacent values immediately preceding and following the missing value.

For the time to response (50% reduction in baseline VAS pain) and the time to first dose of Rescue Medication, patients that do not experience the event within the 48 hour study period will be censored at the end of the period (48.0 hours) and presumed not to have had the appropriate event.

For the Time to Perceptible and Meaningful Pain Relief, a value of 6 hrs indicates that the patient did not experience the event.

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 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.

For participants who withdraw from all study procedures and therefore provide no additional efficacy data beyond the point of withdrawal the primary efficacy endpoint will be imputed using a multiple imputation process. The imputation model will include age, gender and the baseline efficacy measure as well as the post-randomisation measures of the appropriate efficacy outcome, randomised group and the interaction between the post-randomisation efficacy outcome and randomised group.

12 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.

Any revisions to this document prior to database lock will be made in the form of an amendment to the Statistical Analysis Plan. Any deviations or additional analyses that are performed will be summarised in the form of an addendum to the Statistical Analysis Plan. In either case, deviations (subtractions or additions) from the planned statistical analysis will be fully described in the final Clinical Study Report.

13 SUMMARY TABLES, TO INCLUDE BUT IS NOT LIMITED TO

These tables will produce variable summaries within each treatment group and for the total participant population. The summaries will include means, medians, geometric means, frequencies, percentages, ranges, standard deviations and standard errors as appropriate. For the efficacy variables, differences between Maxigesic® IV and the comparator groups will be tabulated along with p-values as applicable.

If efficacy analysis are undertaken on the PP population, these analyses will be summarized in separate table using the same format as outline below.

Baseline Demographic Information
• Age • Gender • Weight • Height • BMI • Race/ethnicity
Baseline Clinical Characteristics
• Medical History • Surgery duration • Baseline VAS pain level • Vital Signs (Systolic Blood Pressure, Diastolic Blood Pressure, Heart Rate, Respiratory Rate and Temperature)
Study Drug Admin & Concomitant Therapy
• Summary of withdrawals (if applicable) • Summary of compliance (study drug usage) • Summary of protocol deviations • Summary of concomitant medications
Primary Endpoint
• Summary of Time-adjusted SPID up to 48 hours (mm)
Secondary Endpoints
• VAS Pain intensity score (mm) at baseline and each scheduled assessment time point after the first dose of study drug • VAS Pain intensity difference (PID) at each scheduled assessment time point after the first dose of study drug • Time-adjusted $SPID_6$, $SPID_{12}$ and $SPID_{24}$ • Total Pain Relief (TOTPAR) including $TOTPAR_6$, $TOTPAR_{12}$, $TOTPAR_{24}$ and $TOTPAR_{48}$ • Response Rate • Time to Response • Time to onset of analgesia using the two-stopwatch method (measured as time to perceptible pain relief confirmed by meaningful pain relief) • Pain relief score on a 5-point categorical scale at each scheduled time point after the first dose of study drug • Peak pain relief • Time to peak pain relief • Proportion of subjects using rescue medication • Time to first use of rescue medication (duration of analgesia) • Total Dose (mg) of primary (oxycodone) and secondary (morphine) rescue medication over first 24 hours, and the full 48 hour study period • Total oral Morphine Milligram Equivalent (MME) dose of all rescue medication over the first 24 hours and the full 48 hour study period • Patient's global evaluation of study drug
Sensitivity Analyses
• Sensitivity Analysis of the primary endpoint (Time-adjusted $SPID_{48}$) • Sensitivity Analyses of imputation of VAS and PR scores

Adverse Events (AEs)
• Frequency/incidence of AEs coded to MedDRA Preferred Term or System Organ Class Code, by study drug and/or relationship, and/or severity • Listings of SAEs • Changes from baseline in Vital Sign measurements (Systolic Blood Pressure, Diastolic Blood Pressure, Heart Rate, Respiratory Rate and Temperature) at the following time points: • End of infusion of first dose • Prior to 5th dose • At discharge on Day 3/early termination

14 REFERENCES

1. Centers for Disease Control and Prevention. Calculating Total Daily Dose of Opioids For Safer Dosage [Internet]. [cited 2017 Jul 7]. Available from: https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf

2. Open Anaesthesia. IV to PO opioids – Equivalency [Internet]. [cited 2017 Jul 7]. Available from: https://www.openanesthesia.org/aba_iv_to_po_opioids_-_equivalency/