APPENDIX 1.9

Documentation of Statistical Methods

The Statistical Analysis Plan is enclosed overleaf. Further information may be provided in the form of a Study Data Reviewer's Guide and an Analysis Data Reviewer's Guide, upon request.

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

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Statistical Analysis Plan

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1 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

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 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 the intravenous route is clinically justified by an urgent need to treat pain or hyperthermia, and/or when other routes of administration are not possible or prudent.

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.

3 STUDY DESIGN AND OBJECTIVES

3.1 Design

This study is a Phase III, multicentre, 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).

Eligible subjects will complete all screening procedures within 30 days prior to the surgery. At screening, subjects will provide written informed consent to participate in the study before any protocol-specified procedures or assessments are completed. At screening, 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
- 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

Patients will undergo either non-laparoscopic general, plastic or orthopedic surgery.

The first dose of Maxigesic® IV (acetaminophen 10 mg/ml + ibuprofen 3 mg/ml in 100 ml solution) will 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 6 hours after the final dose of study drug. The number of doses of study drug, and therefore the length of the treatment period, will be determined 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, 6 hours after the last dose) and prior to discharge.

Subjects may receive supplemental analgesia with an opioid product if pain is not sufficiently controlled by the investigational product.

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.

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.

3.2 Primary Objective

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.

3.3 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

4 GENERAL ANALYSIS DEFINITIONS

4.1 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.

4.2 Participant Populations

4.2.1 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.

4.3 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 6 hours after the last dose, and prior to discharge.

5 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The demographic and baseline clinical characteristics of the study population including age, gender, race, ethnicity, indication (type of surgery), surgery duration, vitals and laboratory values, will be summarized as means, medians, standard deviations, ranges and frequencies and percentages as appropriate. Medical history will be displayed by System Organ Class and Preferred Term.

6 PARTICIPANT DISPOSITION

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.

Exposure will also be presented by age group, race, sex and study site. Early withdrawals for any reason will be tabulated.

7 STUDY MEDICATION AND CONCOMITANT THERAPY

7.1 Compliance

Participants whose study drug usage, or dose rate exceeds the limitations provided by the study protocol will be included in a summary 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 at baseline that continue through the study period and those that commenced during the study will be coded and summarised as frequencies and percentages within ATC-coded drug groups. Baseline and study concomitant medications will be presented in separate tables.

8 SAFETY ANALYSES

8.1 Primary Analyses

The primary endpoint is the incidence of TEAEs associated with exposure to Maxigesic® IV. A TEAE is any AE that starts or worsens during the treatment period. AEs 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.

8.2 Secondary Analyses

8.2.1 Time Course of Treatment-Emergent Adverse Events

TEAEs will be tabulated as frequencies and percentages of subjects receiving at least one dose of the study drug during the following time periods:

- On each day during the treatment period:
    - Day 1
    - Day 2
    - Day 3
    - Day 4
    - Day 5
    - Day 6+
- In addition, AEs during follow-up will be tabulated as frequencies and percentages.

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

If an AE cannot be precisely assigned to a day, for instance because of a missing start time, it will be assigned to the earliest possible day.

8.2.2 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.

8.2.3 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.

8.2.4 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.

8.2.5 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 ($\leq$ 48 hours, 48 hours – 4 days, $\geq$ 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.

Shift tables will also present the number of subjects with low, normal, high or missing laboratory values at baseline along with their shifts at the end of treatment. The number of important shifts (normal to low, normal to high, high to low, low to high) will also be tabulated, along with the number of these which resulted in abnormal values considered clinically significant by the investigator.

8.2.6 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.

8.3 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)
- study site

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

8.4 Other Safety Analyses

8.4.1 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.

8.4.2 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.

8.5 Meta-analysis with MXIV-07 data

Data from the previous study MXIV-07 will be combined with MXIV-11 data, increasing the number of patients in the Maxigesic IV exposure group and allowing comparisons with placebo, ibuprofen and acetaminophen monotherapy treatment. The following endpoints will be repeated with the new combined dataset. Only the first 48 hour period of MXIV-11 will be used in the metanalysis to match the MXIV-07 treatment period.

8.5.1 Demographic and Baseline Characteristics

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

8.5.2 Participant disposition

To evaluate the extent of drug exposure, 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.

8.5.3 Concomitant Medications

Concomitant medications at baseline that continue through the study period and those commenced during the study will be coded and summarised as frequencies and percentages within ATC-coded drug groups. Baseline and study concomitant medications will be presented in separate tables.

8.5.4 Incidence of TEAEs

The incidence of TEAEs associated with exposure to any study drug 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.

8.5.5 Time Course of Treatment-Emergent Adverse Events

TEAEs will be tabulated as frequencies and percentages of subjects receiving at least one dose of the study drug during the following time periods:

- On each day during the first 48 hour treatment period:
    - Day 1
    - Day 2
- In addition, AEs during follow-up will be tabulated as frequencies and percentages.

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

8.5.6 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.

8.5.7 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.

8.5.8 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.

8.5.9 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.

8.5.10 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)
- indication (type of surgery)

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

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

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.

8.6 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.

8.7 Data Collection

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

9 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 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.

Baseline Demographic Information
• **Age** • **Gender** • **Weight** • **Height** • **BMI** • **Race/ethnicity**
Baseline Clinical Characteristics
• **Medical History by SOC and PT** • **Surgery duration** • **Vital Signs (Systolic Blood Pressure, Diastolic Blood Pressure, Heart Rate, Respiratory Rate and Temperature)** • **Laboratory values (hematology/chemistry)** • **Concomitant medications**
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
• **Treatment-Emergent Adverse Events Occurring during the Treatment Period**
Secondary Endpoints
• **Time Course of Treatment-Emergent Adverse Events - Day 1** • **Time Course of Treatment-Emergent Adverse Events - Day 2** • **Time Course of Treatment-Emergent Adverse Events - Day 3** • **Time Course of Treatment-Emergent Adverse Events - Day 4** • **Time Course of Treatment-Emergent Adverse Events - Day 5** • **Time Course of Treatment-Emergent Adverse Events - Day 6+** • **Time Course of Adverse Events - During Follow-up** • **Treatment-Related Adverse Events** • **Treatment-Emergent Adverse Events of Interest** • **Treatment-Related Adverse Events of Interest** • **Changes in Vital Signs** • **Changes in Hematology/Chemistry Values** • **Hematology/Chemistry Summary shift tables - Overall** • **Hematology/Chemistry Summary shift tables - duration of treatment ≤ 48 hours** • **Hematology/Chemistry Summary shift tables - duration of treatment between 48 hours and 4 days** • **Hematology/Chemistry Summary shift tables - duration of treatment ≥ 5 days** • **Patient's Global Evaluation of the Study Drug**
Subgroup Analyses
• **TEAEs by Gender** • **TEAEs by Race** • **TEAEs by Age** • **TEAEs by Duration of Exposure** • **TEAEs by Indication (Type of Surgery)** • **TEAEs by Study Site**
Other Safety Analyses
• **TEAEs by Severity**

• **TEAEs by Relationship to the Study Drug** • **Summary ECG shift tables - overall** • **Summary ECG shift tables - duration of treatment ≤ 48 hours** • **Summary ECG shift tables - duration of treatment between 48 hours and 4 days** • **Summary ECG shift tables - duration of treatment ≥ 5 days**
Meta-analysis tables (MXIV-07 + MXIV-11)
• **Age** • **Gender** • **Weight** • **Height** • **BMI** • **Race/ethnicity** • **Surgery duration** • **Vital Signs (Systolic Blood Pressure, Diastolic Blood Pressure, Heart Rate, Respiratory Rate and Temperature)** • **Baseline Concomitant medications** • **Summary of withdrawals (if applicable)** • **Summary of compliance (study drug usage)** • **Summary of concomitant medications** • **Treatment-Emergent Adverse Events Occurring during the Treatment Period** • **Time Course of Treatment-Emergent Adverse Events - Day 1** • **Time Course of Treatment-Emergent Adverse Events - Day 2** • **Time Course of Adverse Events - During Follow-up** • **Treatment-Related Adverse Events** • **Treatment-Emergent Adverse Events of Interest** • **Treatment-Related Adverse Events of Interest** • **Changes in Vital Signs** • **Patient's Global Evaluation of the Study Drug** • **TEAEs by Gender** • **TEAEs by Race** • **TEAEs by Age** • **TEAEs by Indication (Type of Surgery)** • **TEAEs by Severity** • **TEAEs by Relationship to the Study Drug**