AN OPEN LABEL EXTENSION STUDY TO ASSESS THE SAFETY OF LONG-TERM TREATMENT WITH A 4-ML INTRA-ARTICULAR INJECTION OF AMPION IN ADULTS WITH PAIN DUE TO SEVERE OSTEOARTHRITIS OF THE KNEE

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: AP-003-C-OLE

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STATISTICAL ANALYSIS PLAN APPROVAL SHEET

Protocol Number: AP-003-C-OLE

Product: Ampion™

Protocol Title: An Open Label Extension Study to Assess the Safety of Long-Term Treatment with a 4 ml Intra-Arterial Injection of Ampion™ in Adults with Pain Due to Severe Osteoarthritis of the Knee

AN OPEN LABEL EXTENSION STUDY TO ASSESS THE SAFETY OF LONG-TERM TREATMENT WITH A 4-ML INTRA-ARTICULAR INJECTION OF AMPION™ IN ADULTS WITH PAIN DUE TO SEVERE OSTEOARTHRITIS OF THE KNEE

Author: Gary Stevens, Ph.D

Version: 1.00

Version date: September 11, 2018

Approved by:

Name — Date: 2018-11-15

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An Open Label Extension Study to Assess the Safety of Long-Term Treatment with a 4 ml Intra-Arterial Injection of Ampion™ in Adults with Pain Due to Severe Osteoarthritis of the Knee

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Biostatistician:	Gary Stevens, Ph.D.

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1. INTRODUCTION

This statistical analysis plan (SAP) outlines the proposed statistical methods to be implemented during the review and analysis of the data to ensure confirmation with categories determined by the Case Report Form (CRF) or the anticipated ranges for continuous variables and analysis of data collected within the scope of Ampion Protocol AP-003-C-OLE, "An Open Label Extension Study to Assess the Safety of Long-Term Treatment with a 4 mL Intra-Arterial Injection of Ampion in Adults with Pain Due to Severe Osteoarthritis of the Knee," protocol version 3.0 dated 26 March 2018.

It is not intended that each and every table, listing, or graph will be included in the clinical study report (CSR). It is also possible that additional analyses will be conducted after review of the data. Any analyses or summaries not specified in the SAP, but performed after review of the data, will be identified in the CSR as post hoc.

2. OBJECTIVES

2.1 Primary Objective

The primary trial objective is to carry on from the AP-003-C main study (one injection) and evaluate the safety of a 4-mL intra-articular (IA) injection of Ampion with repeat dosing every 12 weeks for 52 weeks and/or with five total injections of Ampion.

2.2 Secondary Objective

The exploratory objectives are to analyze the efficacy of a 4-mL intra-articular (IA) injection of Ampion with repeat dosing every 12 weeks for 52 weeks and/or with five total injections of Ampion.

2.3 Study Design

Subjects who have completed the AP-003-C main study (n=161) will be offered the option to roll-over to the open label extension study (AP-003-C-OLE) at their final visit of the AP-003-C main study (Visit 7). Enrollment into the AP-003-C-OLE study (Visit 9) allows a 170-day screening window from the AP-003-C main study Visit 7. AP-003-C-OLE study will include the following visits:

Visit 9/Enrollment (Day-170 to Day 0, but not to occur before completion of AP-003-C main study) in-office visit, Visit 10 (24 hours after enrollment post injection follow-up telephone call), Visit 11 in-office visit (Day 84 ±14 days), Visit 12 (24 hours after Visit 11 post injection follow-up telephone call), Visit 13 in-office visit (Day 168 ± 14 days), Visit 14 (24 hours after Visit 13 post injection follow-up telephone call), Visit 15 in-office visit (Day 252 ± 14 days), Visit 16 (24 hours after visit 15 post injection follow-up telephone call), Visit 17 final in-office visit (Day 280 ± 14 days).

The safety of repeat dosing will be evaluated at all visits; in-office visit safety assessments will include vital signs, physical exams, evaluation of AEs, and laboratory analysis. Phone visits will evaluate for AEs.

The clinical effects of treatment on OA pain will be evaluated during all in-clinic visits using the Western Ontario and McMaster Universities Arthritis Index (WOMAC®) osteoarthritis Index 3.1 and the Patient's Global Assessment of disease severity (PGA). The WOMAC will also be utilized to assess the contralateral knee pain at Enrollment/Visit 9 and Visit 17 (or Early Termination Visit).

The WOMAC® is a validated pain scoring system and sets the standard for the subject response. In order not to bias the collection of data, only questions from the validated WOMAC pain scale will be asked of subjects.

2.4 Sample Size

The original AP-003-C study used total of 170 subjects (140 Ampion; 25 Saline) to test the following hypotheses.

$$H_0: \pi \leq 30\% \text{ versus } H_A: \pi > 30\%$$

This study is observational, using subjects who consent from the AP-003-C study, so no formal sample size was calculated. In following ICH E1A safety guidelines to assess clinical safety in long-term treatment of non-life-threatening conditions, it is anticipated that 100 subjects will be enrolled into this study.

3. PRIMARY STUDY ENDPOINTS

3.1 Primary Endpoint

The primary trial endpoint is to evaluate the incidence and severity of treatment-emergent adverse events (TEAEs)

3.2 Exploratory Endpoints

The exploratory endpoints in this trial will be assessed at Visit 9 (Enrollment), Visit 11 (Week 12), Visit 13 (Week 24), Visit 15 (Week 36) and Visit 17 (Week 40) and are:

- Responder status based on the OMERACT-OARSI responder criteria
- Evaluate OMERACT-OARSI 'controlled' responder defined as a 20% improvement in Pain and Function and 0.5 point absolute change in the 5-point Likert Scale
- Evaluate 20% improvement in PGA and 0.5 point absolute change in the 5-point Likert Scale
- Mean change and percent change in WOMAC A pain subscore
- Mean change and percent change in WOMAC B stiffness subscore
- Mean change and percent change in WOMAC C physical function subscore
- Mean change and percent change in PGA

- Mean Change and percent change in WOMAC A pain subscore questions 1 and 2 (pain with movement)
- Mean Change and percent change in WOMAC A pain subscore questions 3–5 (resting pain)
- Change in contralateral knee pain (WOMAC A)
- Change in contralateral knee stiffness (WOMAC B)
- Change in contralateral knee function (WOMAC C)
- Time to Total Knee Replacement (TKR)
- Use of rescue analgesia (amount of acetaminophen used)

4. HYPOTHESES AND METHODS

4.1 Primary Analysis Methodologies

Since this is an observational study on the repeat administration of Ampion 4 mL injection, no formal hypotheses will be tested in this study. There will be no comparisons made to threshold values or to "historical"control values. There is no comparator in this study.

All analyses will be descriptive in nature and will be performed at each efficacy assessment (Visit 9 (Enrollment), Visit 11 (Week 12), Visit 13 (Week 24), Visit 15 (Week 36) and Visit 17 (Week 40)). For dichotomous outcomes, the percentage of patients with that outcome will be estimated and exact 95% binomial confidence intervals will be calculated. These dichotomous outcomes are:

- The incidence of treatment emergent adverse events
- Responder status based on the OMERACT-OARSI responder criteria
- Evaluate OMERACT-OARSI 'controlled' responder defined as a 20% improvement in Pain and Function and 0.5 point absolute change in the 5-point Likert Scale
- Evaluate 20% improvement in PGA and 0.5 point absolute change in the 5-point Likert Scale

The outcomes with more continuous responses will be analyzed via descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Also, 95% confidence intervals from the mean response will be calculated. These outcomes are:

- Mean change and percent change in WOMAC A pain subscore
- Mean change and percent change in WOMAC B stiffness subscore
- Mean change and percent change in WOMAC C physical function subscore
- Mean change and percent change in PGA
- Mean Change and percent change in WOMAC A pain subscore questions 1 and 2 (pain with movement)
- Mean Change and percent change in WOMAC A pain subscore questions 3–5 (resting pain)
- Change in contralateral knee pain (WOMAC A)
- Change in contralateral knee stiffness (WOMAC B)
- Change in contralateral knee function (WOMAC C)

Differences in pain scores between successive visits will be estimated via descriptive statistics and confidence intervals.

The time to total knee replacement will be summarized using Kaplan-Meier methodologies. The use of rescue analgesia will be summarized as the dichotomous outcome on the number of patients using resuce medication and as continuous variables on the number of medications use.

This is an Open Label Extension study, which is designed to assess the safety of patients who have previously completed the main AP-003-C study. It is also desirable to assess the efficacy of all patients relative to their original baseline and first injection and exposure to the investigational product. Thus, the previously mentioned statistics will be calculated using the baseline from the main study, AP-003-C.

4.2 Definition of Study Visits

This clinical trial has a total of 7 study visits, including telephone contacts, during the 52-week study (see Section 10 of this document for details). The time on study for each subject observation will be defined relative to Day 0/Baseline, the day of the initial dose for this study. For analysis, the Baseline measure is the latest measure prior to initiation of treatment.

	Enrollment	Post Treatment Phone Contact	Week 12	Post Treatment Phone Contact	Week 24	Post Treatment Phone Contact
Visit # Day #	9 Day-170 to 0	10 24 hours post Visit 9	11 Day 84± 14 days	12 24 hours post Visit 11	13 Day 168 ± 14 days	14 24 hours post Visit 13

	Week 36	Post Treatment Phone Contact	Week 40 Final Visit	Early Termination
Visit # Day #	15 Day 252 ± 14 days	16 24 hours post Visit 15	17 Day 280 ± 14 days	18 Early Termination

4.3 Number of subjects to receive study drug

It is estimated that approximately 160 subjects will receive a single (1) intra-articular injection of 4 mL Ampion. The injections will be given 12 weeks apart for a series of 4 injections.

4.4 Disposition of subjects

Disposition of subjects, including study completion status and response to therapy as measured by WOMAC subscores and PGA, will be summarized by age group, race, and gender for each of the analysis populations.

4.5 Interim analysis

There will be no interim analysis.

4.6 Blinding and randomization

This is an open-label study where all subjects will receive Ampion 4mL as an intra-articular injection in the study knee.

4.7 Data presentation

4.7.1 Demographic and Baseline Characteristics:

Demographic (e.g., age, sex, race, and ethnicity) and Baseline characteristics (e.g., weight, height, prior injection of another intra-arterial therapeutic for OA of the knee) will be summarized using descriptive statistics, overall and by treatment group for the ITT analysis population.

4.7.2 Medical History and Physical Examination:

The number and percent of subjects with past and current medical disorders at the time of randomization will be presented overall for the ITT analysis population. Results of any abnormalities documented from the abbreviated physical examination at Baseline and Week 40, will be summarized overall for the safety and ITT analysis populations.

4.7.3 Concomitant Medications or Treatments:

The number and percent of subjects receiving concomitant medications or treatments prior to and during the study and at the final visit will be tabulated and presented overall for the ITT analysis population. Concomitant medications/treatments will be

summarized using descriptive statistics and will be presented by type of drug (WHO DRUG classification) overall for the safety and ITT analysis populations.

4.7.4 Safety data:

Safety data will be evaluated by changes in vital sign measurements, physical exam, laboratory analysis, and the frequency and severity of AEs. Concomitant medication will be recorded for safety.

Adverse events:

The Investigator is responsible for monitoring the safety of subjects who have enrolled in the study. All AEs considered related, or possibly related to Ampion, will be followed until the event resolves or stabilized without further change. Subjects will be followed for the occurrence of AEs until 12 weeks after the first dose of study medication.

Investigators are required to document all AEs occurring during the clinical trial, commencing with the first day of treatment through the end of study. AEs should be properly documented on the appropriate CRF pages.

The severity of AEs (mild, moderate, severe), relatedness (related, possibly related, unrelated) along with the duration, action taken, and outcome (e.g., study withdrawal) will also be recorded. In addition, events meeting the criteria of a Serious Adverse Event (SAE) must be reported to the Sponsor within 24 hours on the SAE reporting forms.

4.8 MISSING DATA

All data collected under this study protocol will be included in the assessment of subject safety. Missing or incomplete AE data will assume greatest relationship to study drug and/or severity.

For the exploratory effectiveness endpoints (WOMAC A, WOMAC C, and PGA), missing values will be imputed when the ITT analysis population is used. The Worst Observation Carried Forward (WOCF) will be selected as the primary method of imputing missing data. Alternate imputation methods that may be employed will include multiple imputations (SAS PROC MI and SAS PROC MIANALYZE) and Last Observation Carried Forward (LOCF).

4.9 Detection of Bias

There is no blinding in this study and thus there is never a situation where any breaking of the blind for individual subjects will be necessary.

4.10 Outliers

No formal outlier tests are planned. Values that are outside the pre-defined range, such as a WOMAC score not between zero and four, or a PGA score not between one and five, would be queried and excluded if necessary prior to database lock.

4.11 Testing/Validation Plan

All statistical analyses will be programmed using SAS® software version 9.3, or later. Testing and validation plans for all programs will be developed in accordance with contract research organization guidelines and will include independent programming of tables and analyses.

5. DEFINITIONS

5.1 Abbreviations

Abbreviation	Definition
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical Classification System
CSR	Clinical Summary Report
ICH	International Confernece on Harmonisation
MedDRA®	Medical Dictionary for Regulatory Activities
mL	Milliliter
NA	Not applicable
ng	Nanogram
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
OAK	Osteoarthritis of the knee
OMERACT-OARSI	Outcome measures in rheumatology clinical trials and osteoarthritis research
PGA	Patient's global assessment of disease severity
PP	Per protocol population
SAE	Serious adverse event
SAS	Statistical Software from SAS Institute
SD	Standard deviation
SEM	Standard error of the mean

TEAE	Treatment-emergent adverse event
WO	Washout
WOMAC	Western Ontario and McMaster Universities Arthritis Index

5.2 Definitions

Adverse Event (AE)

An adverse event (AE) is defined as any undesired medical occurrence in a patient or clinical investigation patient receiving a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable sign and unintended sign (including an abnormal laboratory finding comparing pre-treatment to post-treatment), symptom, or disease temporarily associated with the use of a study drug, whether or not related to the study drug.

AEs will be graded for severity using the following categories. Missing grade will be assigned a grade of 3 (severe) in tabulations.

Grade 1 (MILD): The symptom is barely noticeable to the study patient and does not influence performance or functioning. Concomitant medication is not ordinarily indicated for relief of mild AEs.

Grade 2 (MODERATE): The symptom is of sufficient severity to make the study patient uncomfortable and to influence performance of daily activities. Concomitant medication may be indicated for relief of moderate AEs.

Grade 3 (SEVERE): The symptom causes severe discomfort, sometimes of such severity that the study patient cannot continue in the study. Daily activities are significantly impaired or prevented by the symptom. Concomitant medication may be indicated for relief of severe AEs.

Relationship to study drug will be codes using the following categories. Missing relatedness will be assigned to "related" in tabulations.

Unrelated: The adverse event is unlikely to have been caused by study drug.
Possibly related: It is unclear whether the adverse event may have been caused by study drug.
Related: The adverse event is likely to have been caused by study drug.

Serious Adverse Event:

A serious adverse event (SAE) is defined as an adverse event that

- Results in death
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)

- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Treatment-Emergent AE:

A treatment-emergent AE (TEAE) is any AE that begins or increases in severity after the initial dose of study drug.

Age

Subject's age is defined as its integer value in years at enrollment.

Baseline

For any variable, unless otherwise defined, baseline is the last assessment taken prior to the first study drug administration.

Change from Baseline:
The arithmetic difference between a post-baseline value and the baseline value:
Change from Baseline = (Post-baseline Value – Baseline Value)
Percentage Change from Baseline = [(Post-baseline Value – Baseline Value) / Baseline Value] x 100

End of Study

End of study is at Visit 17 (Day 280 ± 14 days), unless terminated early.

Enrollment date

Enrollment date is the same as the randomization date and is designated Day 0.

Study drug

Study drug in this study is Ampion or saline.

Randomization date

Randomization date is the day the subject is assigned a randomization number on study Day 0.

Study Day 0

Day 0 is defined as the first day that study drug is administered to the subject.

Study Day

Day of treatment: study day = (visit date - date of Study Day 0)

6. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

Modifications to the planned statistical analyses should be minimized. Nonetheless, the data obtained from the study may indicate that the planned analyses are inappropriate,

that additional analyses need to be performed, or that the design of the study needs to be modified, due to factors such as the distribution of the data or imbalance in important covariates. The study report will provide a detailed explanation for any deviations from the planned analyses.

7. LIST OF PLANNED TABLES, FIGURES, AND LISTINGS

Tables are categorized and numbered in accordance with ICH E3 guidelines. Each table, figure and listing is presented by treatment arm. All efficacy tables will be provided both for ITT and PP. Accountability tables will also include an overall column. Listings will be sorted by treatment, subject ID, and by visit, if multiple visits exist. These will be provided in a sepeate document.

Number	Title
14.1 Accountability	
14.1.1	Accountability (Analysis Population: All Enrolled)
14.1.2	Enrollment by Site (Analysis Population: All Enrolled)
14.1.3	Analysis Populations (include ITT, safety, PP, and reasons for PP exclusion)
14.1.4	Subject Disposition (all screened)
14.1.5	Major Protocol Deviations (Analysis Population: All Enrolled)
14.1.6.1	Demographics and Baseline Characteristics (Analysis Population: ITT)
14.1.6.2	Demographics and Baseline Characteristics (Analysis Population: PP)
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14.2.1.5	Summary of Patients responding to 50% improvement in Pain and 1.0 absolute change
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14.2.1.7	Summary of Patients responding to a 20% improvement in Pain and 0.5 absolute change
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14.2.1.12	Summary of WOMAC B mean change
14.2.1.13	Summary of WOMAC B percent change
14.2.1.14	Summary of WOMAC C mean change
14.2.1.15	Summary of WOMAC C percent change
14.2.1.16	Summary of WOMAC A and C mean change
14.2.1.17	Summary of WOMAC A and C percent change
14.2.1.18	Summary of PGA mean change
14.2.1.19	Summary of PGA percent change
14.2.1.20	Summary of WOMAC mean change
14.2.1.21	Summary of WOMAC percent change

Number	Title
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14.3.2	Incidence of TEAEs by System Organ Class and Preferred Term (Analysis Population: Safety)
14.3.3	Incidence of Treatment Emergent Related AEs by System Organ Class and Preferred Term
14.3.4	Incidence of Treatment Emergent Serious AEs by System Organ Class and Preferred Term
14.3.5	Incidence of TEAEs by Preferred Term in Descending Order of Frequency
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14.3.10.4	Medication started on study by WHO Preferred Term in Descending Order of Use
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10.3.5	Rescue Med Use Over 12 Weeks

8. LITERATURE CITATIONS / REFERENCES

SAS Institute Inc. SAS Language: version 8 first edition. SAS Institute, Inc, Cary, NC, USA, 1990.

9. HANDLING OF MISSING OR INCOMPLETE DATES FOR ADVERSE EVENTS AND CONCOMITANT MEDICATIONS

9.1 Imputation Rules for Partial or Missing Stop Dates

If the month and year are present, impute the last day of the month. If only the year is present, impute December 31 of that year. If the stop date is entirely missing, assume the event or medication is ongoing. If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or concomitant medication stopped and the stop date will be imputed, if partial.

		Stop Date						
		Complete: yyyymmdd		Partial: yyyymm		Partial: yyyy		Missing
Start Date		<1st Dose	≥1st Dose	<1st Dose yyyymm	≥1st Dose yyyymm	<1st Dose yyyy	≥1st Dose yyyy	
Partial: yyyymm	=1st Dose yyyymm	2	1	2	1	N/A	1	1
	≠ 1st Dose yyyymm		2		2	2	2	2
Partial: yyyy	=1st Dose yyyy	3	1	3	1	N/A	1	1
	≠ 1st Dose yyyy		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose
2 = Impute the first of the month
3 = Impute January 1 of the year
4 = Impute January 1 of the stop year

Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month.

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

10. SCHEDULE OF ASSESSMENTS AND PROCEDURES

	Enrollment	Post Treatment Phone Contact	Week 12	Post Treatment Phone Contact	Week 24	Post Treatment Phone Contact	Week 36	Post Treatment Phone Contact	Week 40 Final Visit	Early Termination
Visit # Day #	9 Day-170 to 0	10 24 hours post Visit 9	11 Day 84± 14 days	12 24 hours post Visit 11	13 Day 168 ± 14 days	14 24 hours post Visit 13	15 Day 252 ± 14 days	16 24 hours post Visit 15	17 Day 280 ± 14 days	18 Early Termination
Informed Consent	X									
Inclusion/exclusion criteria	X									
Medical history/prior medications[2]	X						X			X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Physical examination	X		X		X		X		X	X
Vital Signs	X		X		X		X		X	X
WOMAC	X		X		X		X		X	X
Patient's global assessment (PGA)	X		X		X		X		X	X
X-ray[1]	X								X	X
Clinical laboratory tests	X								X	X
Urinalysis	X									
Treatment with study drug	X		X		X		X			
Rescue medication dispensed	X		X		X		X		X	X
Review Rescue medication	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X