A PHASE 3 RANDOMIZED STUDY TO CONFIRM THE EFFICACY OF AN INTRA-ARTICULAR INJECTION OF AMPION™ IN ADULTS WITH PAIN DUE TO SEVERE OSTEOARTHRITIS OF THE KNEE

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: AP-003-C

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STATISTICAL ANALYSIS PLAN APPROVAL SHEET

Protocol Number: AP-003-C

Product*:* Ampion™

Protocol Title: A Phase 3 Randomized Study to Confirm the Efficacy of an Intra-Articular Injection of Ampion™ in Adults with Pain Due to Severe Osteoarthritis of the Knee

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Name	Date

STATISTICAL ANALYSIS PLAN

A Phase 3 Randomized Study to Confirm the Efficacy of an Intra-Articular Injection of Ampion™ in Adults with Pain Due to Severe Osteoarthritis of the Knee Protocol Number AP-003-C

Version:	2.00
Date:	14 November 2017
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 CRF or the anticipated ranges for continuous variables and analysis of data collected within the scope of Ampion Protocol AP-003-C, "A Phase 3 Randomized Study to Confirm the Efficacy of an Intra-Articular Injection of Ampion™ in Adults with Pain Due to Severe Osteoarthritis of the Knee," protocol version 1.3 dated 09 November 2017.

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 evaluate the clinical efficacy of a single intra-articular injection (4 mL) of Ampion.

2.2 Secondary Objective

The secondary trial objectives is to evaluate the safety of a single intra-articular injection (4 mL) of Ampion.

2.3 Study Design

This is a randomized, double-blind study with a 7-day screening period for each patient followed by a 12-week participation period. A total of 171 subjects with osteoarthritis of the knee (OAK) will be randomized 6:1 across 2 study arms, 4 mL Ampion™ and 4 mL saline. Deferred treatment of pain in the most severe form of the disease is unacceptable to both patients and physicians, and a larger saline arm is not possible or necessary for true comparator purposes in severe OAK subjects. The saline arm is for control of unintended bias and is not intended for analysis; only the active Ampion arm will be analyzed for efficacy.

Severe OAK is a painful, incurable, and progressive disease with a highly predictable outcome. Methodological challenges exist in this debilitated patient population where an unmet medical need exists and there is no valid, licensed or approved control or therapy for severe OAK patients. Therefore, in addition to the 6:1 randomization that is in place to eliminate any unintended bias, the study plan will assess a historic control using all the severe OAK saline-treated patients from all previously completed, randomized, saline-controlled, single-injection Ampion studies. The historic control for this clinical trial has a similar demographic and concomitant treatment profile to the current study, which

allows an effective comparison. Analysis of Ampion and its comparison to this historic saline-control group will ensure a meaningful comparison and quantitative assessment of Ampion effect, in addition to the demonstration of an effect of at least some minimum size, which is considered essential for acceptance of efficacy, specifically in cases where the active control is not a licensed product (e.g. some vaccine trials, IGIV trials, etc.).

The clinical effects of treatment on OAK pain will be evaluated during clinic visits at 6 and 12 weeks, and telephone contacts at 2, and 10 weeks, 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® is a validated scoring system and sets the standard for the patient response. In order not to bias the collection of data, only questions from the validated WOMAC scale will be asked of subjects.

Clinical benefit will be established by significant improvement on the WOMAC Index 3.1 and the PGA as assessed at Weeks 2, 6, 10, and 12. Safety will be assessed by recording adverse events (through 24 hours post-dose and at all follow up contacts) and physical examination and vitals (Baseline, Weeks 6, and 12), and clinical laboratory tests (Screening and Week 12).

2.4 Sample Size

A total of approximately 171 subjects (146 Ampion; 25 Saline) will be enrolled in the study to a single (1) intra-articular injection of 4 mL Ampion or 4 mL saline (6:1).

The sample size for this study is based on the primary endpoint and is based on the following hypotheses.

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

A sample size of 146 patients in the active Ampion arm yields a greater than 90% power of rejecting the null hypothesis when the anticipated proportion under the alternative hypothesis is 45%. This power is applicable for the demonstration of an effect of at least some minimum size, defined in the current trial as greater than a 30% responder rate.

3. PRIMARY STUDY ENDPOINTS

3.1 Primary Endpoint

The primary trial endpoint is to evaluate improvement of OMERACT-OARSI response of a single 4 mL Ampion™ intra-articular injection from Baseline to Week 12.

A patient in this study will be considered an OMERACT-OARSI responder for the purpose of efficacy analysis if the following criteria is met:

1) The patient has a percent improvement in pain (WOMAC pain) from baseline of ≥50% and an absolute change in pain from baseline of ≥ 1 point or the patient has a percent improvement in function (WOMAC function) from baseline of ≥50% and an absolute change in function from baseline of ≥1 point. Meeting this criterion designates the patient as a responder. If the patient does not meet this criterion, then

2) The patient demonstrates improvement in at least 2 of the following:

    - Improvement in pain (WOMAC A) over baseline of ≥20% and a 0.5 point absolute change in pain

    - Improvement in function (WOMAC function) over baseline of ≥20% and a 0.5 point absolute change in function

    - Improvement in patient global assessment (PGA) over baseline of ≥20% and a 0.5 point absolute change in PGA

3.2 Secondary Endpoints

The secondary trial endpoints are to evaluate improvement in a composite endpoint of pain and function, defined as OMERACT-OARSI "controlled" responder, supported by patient global assessment following a single 4 mL Ampion intra-articular injection from Baseline to Week 12.

Secondary endpoints are to evaluate improvement of:

- OMERACT-OARSI "controlled" response from Baseline to Week 12
- PGA response from Baseline to Week 12
- OMERACT-OARSI "controlled" responder from Baseline to Week 12 in comparison to historic saline

A patient in this study will be considered an OMERACT-OARSI "controlled" responder for the purpose of efficacy analysis if the following criteria is met:

1) The patient demonstrates improvement in <u>both</u>:

    - Improvement in pain (WOMAC A) over baseline of ≥20% and a 0.5 point absolute change in pain

    - Improvement in function (WOMAC function) over baseline of ≥20% and a 0.5 point absolute change in function

A patient in this study will be considered to have a PGA response if the following criteria is met:

    - Improvement in patient global assessment (PGA) over baseline of ≥20% and a 0.5 point absolute change in PGA

4. HYPOTHESES AND METHODS

4.1 Primary Hypothesis

Demonstration of an effect of at least some minimum size is considered essential for acceptance of efficacy, and this is defined in the current trial as a greater than 30% responder rate based on review of KOL opinion, literature, and clinical benefit in severely diseased OAK patients. For the primary endpoint of the proportion of patients who are responders to the OMERACT-OARSI criteria from above, the following hypothesis will be tested.

$$H_0: \pi \leq \pi_0 \text{ versus } H_A: \pi > \pi_0$$

Where π_0 is the hypothesized clinically significant value for the proportion of responders. The value will be 30% in this study. This test will be tested using an exact binomial test. That is, given the sample size of n, the number of responders X, and the value of π_0 =0.30, then probability that X or more events would be observed will be calculated as the p-value. Since this is a one-sided test, the alpha level will be 0.025.

4.2 Secondary Hypotheses

The primary hypothesis and these secondary hypotheses will be tested in a hierarchical manner with the primary first and the secondary hypotheses in the order listed. Using this approach, there is no adjustment necessary in the overall significance level. All testing will be conducted using an overall significance level of 5%. If the tests are one sided, the significance level will be 2.5%.

For the secondary endpoint of the proportion of patients who are "controlled responders" to the OMERACT-OARSI criteria as defined in section 3.2 above, the following hypothesis will be tested.

$$H_0: \pi \leq \pi_0 \text{ versus } H_A: \pi > \pi_0$$

Where π_0 is the hypothesized clinically significant value for the proportion of responders. The value will be 30% in this study. This test will be tested using an exact binomial test. That is, given the sample size of n, the number of responders X, and the value of π_0 =0.30, then probability that X or more events would be observed will be calculated as the p-value. Since this is a one sided test, the alpha level will be 0.025.

This composite analysis of OMERACT-OARSI "controlled responder" will be supported by Patient Global Assessment. Patient Global Assessment will be tested against the same hypothesis:

$$H_0: \pi \leq \pi_0 \text{ versus } H_A: \pi > \pi_0$$

The 3rd secondary trial endpoint, evaluating the improvement in a composite endpoint of pain and function (WOMAC A and C), defined as OMERACT-OARSI "controlled" response, will demonstrate that the active arm from this study is superior to analysis of all

historic saline-control arms from previous single-injection Ampion studies, will be analyzed using the following hypothesis.

$$H_0: \pi_A \leq \pi_{HS} \text{ versus } H_A: \pi_A > \pi_{HS}$$

Where π_A is the response rate from Ampion in this study and π_{HS} is the response rate of the saline control from previous single-injection Ampion studies. This will be tested using Fisher's exact test.

4.3 Exploratory Analysis

If it is deemed to be clinically relevant, the analyses will be conducted using the appropriate adjustment methodologies.

4.4 Definition of Study Visits

This clinical trial has a total of 7 study visits during the 12-week study (see Table 6.2). The time on study for each subject observation will be defined relative to Day 0/Baseline, the day of the initial dose. For analysis, the Baseline measure is the latest measure prior to initiation of treatment.

4.5 Number of subjects to receive study drug

A total of approximately 171 subjects (146 Ampion; 25 Saline) will be enrolled in the study to a single (1) intra-articular injection of 4 mL Ampion or 4 mL saline (6:1).

4.6 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.

4.7 Interim analysis

There will be no interim analysis.

4.8 Blinding and randomization

All subjects will be randomized 6:1 to receive Ampion 4 mL or saline 4 mL as an intra-articular injection in the study knee.

4.9 Data presentation

4.9.1 Demographic and Baseline Characteristics:

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

4.9.2 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 12, will be summarized overall for the safety and ITT analysis populations.

4.9.3 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. Concomitant medication and treatment data for the historic control will be provided and summarized.

4.9.4 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 stabilizes 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.

4.10 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 primary effectiveness endpoints (WOMAC A, WOMAC C, and PGA), missing Week 12 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 12 Week data. Alternate imputation methods employed will include multiple imputations (SAS PROC MI and SAS PROC MIANALYZE) and Last Observation Carried Forward (LOCF). These sensitivity analyses will be conducted for the primary effectiveness endpoint, to ensure that the primary method of imputation chosen is robust with respect to imputation method

4.11 Detection of Bias

Any breaking of the blind for individual subjects prior to formal unblinding will be documented in the clinical study report. Reason for unblinding will also be documented. Data collected after unblinding will be noted.

4.12 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.

4.13 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 statistical 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 Conference 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-Osteoarthritis Research Society International
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 coded 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 9 (day 84 ± 7 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 separate 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)
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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

	Screening	Baseline Randomization Treatment	Post-treatment check (telephone contact)	Week 2 (telephone contact)	Week 6	Week 10 (telephone contact)	Week 12 Final Visit	Early Termination
Visit # Day #	**1 Day-28 to 0**	**2 Day 0**	**3 Day 1**	**4 Day 14 ± 7**	**6 Day 42 ± 7**	**8 Day 70 ±7**	**9 Day 84 ± 7**	
Informed Consent	X							
Inclusion/exclusion criteria	X	X						
Medical history/prior medications[2]	X						X	X
Concomitant medications	X	X	X	X	X	X	X	X
Physical examination	X	X			X		X	X
Vital Signs	X	X			X		X	X
Randomization		X						
WOMAC	X	X		X	X	X	X	X
Patient's global assessment (PGA)	X	X		X	X	X	X	X
X-ray[1]	X							
Clinical laboratory tests	X						X	
Treatment with study drug		X						
Rescue medication dispensed		X						
Review Rescue medication			X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X

Visits are in clinic except for Day 1 and Weeks 2 and 10 when subjects will be contacted by telephone

1 X-ray must be acquired at Screening to satisfy inclusion criteria, "Index knee must be symptomatic for greater than 6 months with a clinical diagnosis of OA and supported by radiological evidence (Kellgren Lawrence Grade IV)

2 At Week 12 and Early Termination visits, ask subject if they have previously sought out treatment for OAK prior to this study.