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

STUDY NUMBER: AP-003-C

NCT 03182686

9 November 2017

CLINICAL STUDY PROTOCOL

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

STUDY NUMBER: AP-003-C

Drug Development Phase:	Phase 3
Investigational Product:	Ampion™
Indication:	Severe Osteoarthritis of the knee
Sponsor:	Ampio Pharmaceuticals, Inc. 373 Inverness Parkway, Suite 200 Englewood, CO 80112
Date:	Version 1.3 09 November 2017

Conduct: In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

PROTOCOL SIGNATURE PAGE

I have read, understood, and agree to comply with the contents of this clinical protocol, Study No. AP-003-C version 1.3 dated 09 November 2017, and agree to meet all obligations as detailed in all applicable regulations and guidelines.

Signed by:

<Study personnel signature> **<Enter date>**

<Printed name>

PROTOCOL SYNOPSIS

Sponsor:	**Investigational Product:**	**Developmental Phase:**
Ampio Pharmaceuticals, Inc.	Ampion™	Phase 3

Title of Study:

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

Study Center(s):

Approximately 14 sites

Indication:

Severe osteoarthritis (OA) of the knee (Kellgren Lawrence Grade 4)

Number of subjects:

171 subjects total

Objectives:

The primary trial objective is to evaluate the efficacy of a single 4 mL Ampion™ intra-articular injection.

The secondary trial objective is to evaluate the safety of an intra-articular injection of Ampion

Sponsor:	Investigational Product:	Developmental Phase:
Ampio Pharmaceuticals, Inc.	Ampion™	Phase 3

Methods:

The study will have a 7-day screening period for each patient followed by a 12-week participation period. A total of 171 subjects with knee pain and decreased function due to severe osteoarthritis of the knee (KL IV) will be enrolled. In order to reduce the potential for bias in reporting outcomes, subjects will be randomized 6:1 (Ampion intra-articular injection or saline intra-articular injection). Study visits will include: Screening visit, Baseline, a 24-hour, post-injection follow up call, Week 2 phone visit, Week 6, Week 10 phone visit, and Week 12 for a total of 7 visits. Screening, Baseline, Week 6 and Week 12 are in-office visits.

The clinical effects of Ampion treatment on OA pain, function and PGA will be evaluated during in-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®), and the Patient's Global Assessment of disease severity (PGA).

The WOMAC® is a validated osteoarthritis 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 scale and PGA will be asked of subjects.

Clinical benefit will be established by evaluation of OMERACT-OARSI using the WOMAC 5-point Likert scale and PGA as assessments during the in-office visits and phone visits. Safety will be assessed by recording adverse events (post-injection and at all follow up contacts), physical examination and vitals (Baseline, Weeks 6 and 12), and laboratory tests (Screening and Week 12).

Diagnosis and Main Criteria for Inclusion:

1. Able to provide written informed consent to participate in the study;
2. Willing and able to comply with all study requirements and instructions of the site study staff;
3. Male or female, 40 years to 85 years old (inclusive);
4. Must be ambulatory;
5. Study knee must have a clinical diagnosis of OA supported by radiological evidence (Kellgren Lawrence Grade 4) which is assessed locally (x-rays within the past 6 months of screening are acceptable);
6. Moderate to moderately-severe OA pain in the study knee (rating of at least 1.5 on the WOMAC A, 5-point Likert pain subscale);
7. Moderate to moderately-severe OA function in the study knee (rating of at least 1.5 on the WOMAC C, 5-point Likert Function subscale);
8. WOMAC A, 5-point Likert pain subscale <1.5 in the contralateral knee;
9. Ability to discontinue NSAID use at Screening visit and/or 72 hours prior to the Baseline visit and for the duration of the clinical study (low-dose Aspirin (81 mg) is allowed during the study);
10. No analgesia (including acetaminophen) taken 24 hours prior to an efficacy measure;
11. No known clinically significant liver abnormality (e.g. cirrhosis, transplant, etc.).

Main Criteria for Exclusion:

Sponsor:	**Investigational Product:**	**Developmental Phase:**
Ampio Pharmaceuticals, Inc.	Ampion™	Phase 3

1. As a result of medical review and screening investigation, the Principal Investigator considers the subject unfit for the study
2. A history of allergic reactions to human albumin (reaction to non-human albumin such as egg albumin is not an exclusion criterion)
3. A history of allergic reactions to excipients in 5% human albumin (N-acetyltryptophan, sodium caprylate)
4. Presence of tense effusions
5. Inflammatory or crystal arthropathies, acute fractures, history of aseptic necrosis or joint replacement in the affected knee, as assessed locally by the Principal Investigator
6. Isolated patella femoral syndrome, also known as chondromalacia
7. Any other disease or condition interfering with the free use and evaluation of the study knee for the duration of the trial (e.g. cancer, congenital defects, spine osteoarthritis)
8. Major injury to the study knee within the 12 months prior to screening
9. Severe hip osteoarthritis ipsilateral to the study knee
10. Any pain that could interfere with the assessment of study knee pain (e.g. pain in any other part of the lower extremities, pain radiating to the knee)
11. Any pharmacological or non-pharmacological treatment targeting OA started or changed during the 4 weeks prior to randomization or likely to be changed during the duration of the study
12. Pregnancy or planning to become pregnant during the study.
13. Use of the following medications:
    a. No IA injected medications in the study knee during the study. No Hylauronic Acid (HA) injections in the study knee at least 12 weeks prior to Baseline. No steroid injections in the study knee at least 4 weeks prior to Baseline.
    b. No analgesics containing opioids.
    c. NSAIDs are not permitted during the study; acetaminophen is available as a rescue medication during the study from the provided supply.
    d. No topical treatment on the study knee during the study
    e. No significant anticoagulant therapy (e.g. Heparin or Lovenox) during the study (treatment such as low-dose Aspirin (81 mg) and Plavix are allowed)
    f. No systemic treatments that may interfere with safety or efficacy assessments during the study
    g. No immunosuppressants
    h. No use of systemic or intra-articular corticosteroids
14. No human albumin treatment in the 3 months before randomization or throughout the duration of the study

Test Product, Dose and Mode of Administration:

Ampion, 4 mL, single intra-articular injection in the knee

Reference Therapy, Dose and Mode of Administration:

Saline 4 mL; single intra-articular injection in the knee

Sponsor:	**Investigational Product:**	**Developmental Phase:**
Ampio Pharmaceuticals, Inc.	Ampion™	Phase 3

Study Duration:

12 weeks

Criteria for Evaluation:

Efficacy:
WOMAC Osteoarthritis Index 3.1, 5-point Likert scale Patient Global Assessment

Safety:
Safety will be assessed by recording adverse events (post-injection and at all follow-up contacts), change in laboratory analysis (Screening to Week 12), physical examination and vitals (Baseline, Weeks 6 and 12).

Clinical Endpoints:

Primary Efficacy Endpoint:

- Evaluate improvement of OMERACT-OARSI response of a single 4 mL Ampion intra-articular injection from Baseline to Week 12

Secondary Efficacy Endpoints:

- Evaluate improvement in the composite endpoint of pain and function (WOMAC A and C) from Baseline to Week 12
- Evaluate improvement in PGA from Baseline to Week 12
- Evaluate improvement in the composite endpoint of pain and function (WOMAC A and C), compared to saline from all single-injection Ampion studies

Statistical Methods:

For the primary endpoint evaluating the proportion of patients who are OMERACT-OARSI responders, the following hypothesis will be tested.

$H_0: \pi \leq \pi_0$ versus $H_A: \pi > \pi_0$

Where π_0 is the hypothesized 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 $\pi_0 = 0.30$, 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.

Blinding and Randomization

Subjects will be assigned in a 6:1 ratio to treatment by a randomization schedule developed and maintained by an independent statistician. Ampion and saline will be provided in blinded

study vials labeled with the appropriate information and packed into patient kits. Each patient kit will contain labeled vials, blinded for drug content, syringes, needles and rescue medication.

The Sponsor, the investigator, and all study staff having a role in the day-to-day conduct of the study will remain blinded to treatment.

A comprehensive presentation of the data management and statistical analysis plan will be approved by Ampio Pharmaceuticals, Inc. prior to unblinding of study data.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
°C	degrees Celsius
°F	degrees Fahrenheit
µg	Microgram
ACR	American College of Rheumatology
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase (SGPT)
ARDS	adult respiratory distress syndrome
AST	aspartate transaminase (SGOT)
BP	Blood pressure
CFR	Code of Federal Regulations
CI	confidence interval
Cm	Centimeter
CRF	case report form
CRO	Clinical Research Organization
Da	Dalton
DA-DKP	Asp-Ala diketopiperazine
dL	Deciliter
eDC	electronic data capture
FDA	Food and Drug Administration
G	$11.26 \times (RPM/1000)^2 \times$ Radius (cm)
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	Gastrointestinal
HSA	human serum albumin
HCG	Human chorionic gonadotropin
IA	intra-articular
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
kDa	Kilodalton
KL	Kellgren Lawrence
LDH	lactic dehydrogenase
LK	Likert
MCH	mean cell hemoglobin
MCHC	mean cell hemoglobin concentration
MCID	Minimal Clinically Important Difference
MCV	mean cell volume
Mg	Milligram
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

Abbreviation	Definition
PP	per protocol population
Radius	distance (in centimeters) from the center of rotation to the bottom of tube in the rotor
Rap-1	Regulatory protein
RBC	red blood cell
REB	Research Ethics Board
RPM	Rounds Per Minute
SAE	serious adverse event
SD	standard deviation
SEM	standard error of the mean
SMC	Safety Monitoring Committee
SOP	standard operation procedure
TEAE	treatment-emergent adverse event
TEER	trans endothelial electrical resistance
VAS	Visual Analog Scale
WBC	white blood cell
WCC	white cell count
WO	Washout
WOMAC	Western Ontario and McMaster Universities Arthritis Index

1 INTRODUCTION

HSA has a long history of clinical use as a colloid replacement therapy, dating back over 60 years. Currently, HSA is approved for the indications of hypovolemia, hypoalbuminemia, prevention of central volume depletion after paracentesis due to cirrhotic ascites, ovarian hyperstimulation, adult respiratory distress syndrome (ARDS), acute nephrosis, hemolytic disease of the newborn and burns. In addition to its effects on oncotic pressure, HSA has pharmacological effects including decreased inflammation (Quinlan 2005), decreased vascular permeability (Evans 2002) and no adverse effect on cardiac safety (Vincent JL, 2004).

Ampion™, the < 5 kilodalton (kDa) ultrafiltrate of 5% human serum albumin (HSA), is being developed to provide relief for the pain of severe osteoarthritis of the knee. There are no currently FDA approved drugs for the indication of pain from severe (KL 4) osteoarthritis of the knee for which Ampion is indicated. Ampion is a heterogeneous solution that contains several known small molecules and unknown components that may act synergistically. The individual contribution(s) of the unknown components to the biologic activity of Ampion may not be quantifiable since over 1200 peptides and proteins have been identified in commercial HSA preparations [Gay, 2010].

Bar-Or et al found that commercial preparations of HSA are heterogeneous in terms of posttranslational modifications, including C- and N-terminal truncation, cysteinylation, glycation and nitrosylation (Bar-Or D, 2005). An important modification is the cleavage of the two N-terminal amino acids Aspartate (D) and Alanine (A). This occurs by the action of a naturally occurring dipeptidase (Bar-Or 2013) present in plasma and also bound to or associated with leukocytes and endothelial cells (Ohnuma 2006), and activated during the FDA required heat-treatment of commercial preparations of HSA. After cleavage, the dipeptide undergoes cyclisation to form a diketopiperazine (aspartylalanyl diketopiperazine [DA-DKP]). DA-DKP is found in the low molecular weight fraction (< 5000 Da) of commercial lots of HSA at concentrations ranging from approximately 100 µM.in vitro studies and its action in human subjects suggest that it is an active ingredient in the pharmacological effects of HSA and of Ampion™. Other components, such as N-acetyl tryptophan and its metabolites and sodium caprylate present in HSA and Ampion, act synergistically with DA-DKP on numerous molecular pathways involved in inflammation, nociceptive and neuropathic pain, vascular permeability and the resolution of inflammation in various cell types including synoviocytes, chondrocytes, PBMC, macrophages, memory T cells, endothelial cells and mesenchymal stem cells (Thomas, GW 2016) (Fredrick ED 2016) (Bar-Or 2015) (Shimonkevitz 2008) (Bar-Or 2006) (Bar-Or 2005)

1.1 STUDY DRUG

Ampion™ is the < 5 kDa ultrafiltrate of 5% HSA.

1.2 BACKGROUND TO THE DISEASE

Osteoarthritis (OA) remains a leading contributor to global disability, with both hip and knee OA accounting for over 17 million years lived with disability (Cross 2014). OA is the most common form of arthritis and affects up to 38 million adults in the US alone. OA is caused by inflammation of the soft tissue and bony structures of the joint which worsens over time and leads to progressive thinning of articular cartilage, narrowing of the joint space, synovial membrane thickening, osteophyte formation and increased density of subchondral bone. These changes eventually result in chronic pain and disability and deterioration of the joint despite drug therapy may require eventual surgery for total joint replacement. OA of the knee is defined in stages as noted by Kellgren Lawrence grading: Grade 0 (normal knee; no osteophytes or joint space narrowing), Grade 1 (possible osteophytic lipping and doubtful narrowing of joint space), Grade 2 (definite osteophytes and possible narrowing of joint space), Grade 3 (moderate multiple osteophytes, definite narrowing of joint space and some sclerosis, and possible deformity of the bone ends) and Grade 4 (large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone ends).

Patients with severe OAK, defined radiologically as KL grade 4, have few treatment options for pain management. Even with reported difficulties in managing symptoms, including pain, a large number of KL 4 patients do not discuss pain or OA during consultations. Many patients perceived that they just had to put up with pain until their joint replacement because there was nothing else that could be done (McHugh 2007). The net result is that the patients control their pain by limiting their activity, and this can progress to the point of losing the ability to ambulate in the community. There is a consequent loss of the benefits of activity and the conditioning that this provides, leading to a deterioration of health in general, including both physical and psychological effects (Cisternas 2016). Difficult-to-treat pain conditions, such as severe OAK, are a challenge for both medical and surgical doctors and patients. There is no doubt that patients with chronic pain in general suffer from an unmet need, as FDA agreed stating that there is an unmet medical need among patients with severe osteoarthritis.

The pain associated with osteoarthritis is now thought to be multifactorial. The pathogenesis of pain from OA is comprised of both nociceptive and neuropathic pain pathways resulting from severely damaged cartilage, exposed subchondral bone, joint innervation, and less defined pathways including the synovium. A recent publication in January 2016 (Akinci 2016) noted that the balance between nociceptive and neuropathic pain shifts towards neuropathic pain as the severity of the condition increases. The multifactorial nature of the pain of osteoarthritis may make pain control more difficult, particularly in patients with severe OA (KL4)

The presence of synovitis in KL 4 patients indicates active ‘inflammatory’ disease process. These findings were supported with a linear observation of an increasing trend correlated with the severity of synovitis related to advancing KL grades. Additionally, KL 4 patients have been shown to have lesions that fluctuate with pain, (i.e., fluctuating bone marrow lesions and synovitis) related to a high grade of cartilage loss in KL 4 patients (Guermazi 2015). These findings were further supported using a unique *in vivo* imaging technique that detected activated and not resting macrophages (Kraus 2016). In a patient cohort that included patients

with severe (KL 4) OAK, the quantity of knee-related activated macrophages was statistically associated with more severe knee pain and radiographic severity of knee OAK.

These data demonstrated that greater macrophage mediated inflammation is a cause of more severe pain in KL 4 OAK and provides a rationale whereby Ampion, demonstrated *in vitro* with anti-inflammatory and anti-macrophage activity, may mediate symptomatic relief in this patient group. These data further demonstrate the need to examine patients by disease severity and supply treatment options for severely diseased patients (Guermazi 2015). Ampion has shown anti-inflammatory activity in vitro against macrophages, monocytes, and immune cells.

When the clinical trials of Ampion were designed, it was assumed that the vehicle for the product, saline, would have little to no effect in reducing pain, stiffness, or improving physical function. This control was determined not to be a true placebo, but rather turned out to be active treatment.

The Osteoarthritis Research Society International (OARSI) and Standing Committee for Clinical Trials Response Criteria Initiative Outcome Measures in Rheumatology (OMERACT) committee, in concert with the international rheumatology community, worked to develop a uniform core set of outcome measures for osteoarthritis. While the committee initially developed two sets of responder criteria to present the results of changes after treatment in three symptomatic domains (pain, function, and patient's global assessment) as a single variable for clinical trials, the committee ultimately worked to create a simplified set of responder criteria, Scenario D, which captured the criteria for response.

In the original plan, for each domain, a response was defined by both a relative and an absolute change, with different cut-offs with regard to the drug, the route of administration and the OA localization. The formal OMERACT-OARSI scenarios defined a responder as

a. having achieved a high degree of improvement in pain or a moderate degree of improvement in 2 of the 3 response domains (pain, function, global assessment) (scenario A) OR

b. as having achieved a high degree of improvement in either pain or function, or a moderate degree of improvement in 2 of the 3 response domains (scenario B)

The composite index permits presentation of results of symptom modifying clinical trials in OA based on individual patient responses (responder yes/no). The use of composite indices was still somewhat controversial in that the original OARSI criteria did not account for multiplicity of comparisons, however OMERACT-OARSI worked to rectify this and their conclusions were presented at the OMERACT 6 conference.

OMERACT and OARSI established a task force aimed at evaluating: (1) the variability of observed placebo and active treatment effects using the OARSI responder criteria; and (2) the possibility of proposing a simplified set of criteria. Because individual study endpoints in studies of NSAIDs in patients with hip or knee osteoarthritis were highly correlated, OMERACT-OARSI evaluated six different scenarios to determine whether a simplified set of criteria could be developed. The conclusions of the task force were presented and discussed during the OMERACT 6 conference, where a simplified set of responder criteria (OMERACT-OARSI set of criteria) was proposed. Scenario D was chosen by the members, indicating the importance of having both a relative change and an absolute change as part of the criteria for response.

The criteria for a responder using the Likert Scale, where the 20-point change on the VAS scale is the same as a 1-point change on the Likert Scale and, similarly, the 10-point change in the VAS scale is the same as a 0.5-point change on the Likert Scale, are defined as:

1. High improvement in pain or in function ≥ 50% and absolute change in Likert pain scale of ≥1 OR
2. Improvement in at least two of the 3 following:
    a. pain ≥ 20% and absolute change in Likert score ≥0.5
    b. function ≥ 20% and absolute change in Likert score ≥0.5
    c. patient's global assessment ≥ 20% and absolute change in Likert score ≥0.5

1.3 PREVIOUS HUMAN EXPERIENCE

In addition to the extensive clinical experience with HSA, Ampio Pharmaceuticals, Inc. has completed multiple clinical studies to evaluate the treatment effect of Ampion in subjects with OAK. These studies are summarized in Section 1.5.

1.4 PRECLINICAL DATA

1.4.1 Pharmacology Studies

In vitro pharmacology studies demonstrated that a low molecular weight fraction (< 3000 daltons [Da]) of more than five commercial preparations of HSA, and a cyclized dipeptide contained in that fraction, Asp-Ala diketopiperazine (DA-DKP) have a range of anti-inflammatory properties, which may be expected to ameliorate the symptoms of inflammation, including pain, in man (Bar-Or et al 2006). These studies showed reduced inflammatory cytokine production from human T lymphocytes *in vitro* via modulation of signal transduction through increased expression of Rap-1, and inhibition of macrophage activation. In addition, DA-DKP enhanced integrity of human endothelial cell junctions in the transendothelial electrical resistance (TEER) assay, which would result in decreased vascular permeability to the influx of inflammatory cells *in vivo*. No pharmacokinetics studies were performed as the plasma levels of the constituents of the < 5000 Da preparation, including DA-DKP, after intra-articular injection of a therapeutic dose in man or in laboratory animals are anticipated to be below the limits of detection. For more information, consult the Investigator Brochure.

1.4.2 Toxicity and Safety Studies

HSA and other components of serum albumin preparations are species specific and may be expected to be immunogenic if repeatedly injected into non-human species, even at very low concentrations. For this reason, it was not possible to perform formal toxicological studies in animals.

1.5 CLINICAL EXPERIENCE

Ampio has conducted multiple clinical studies to evaluate the treatment effect and safety of Ampion in subjects with OAK. Ampion has been administered across 6 clinical studies as a single intra articular (IA) injection or as three IA injections administered every two weeks. 3 single-dose pivotal Phase 3 studies, 2 multi-dose studies, and 1 multiphase single-dose phase 1b study have been completed. An overview of the efficacy studies is provided in the Table 1.5.1

For the clinical development program, all studies were conducted in subjects with moderate to moderately severe pain due to OA of the knee. Patients were required to have x-ray findings demonstrating KL grade 2, 3, or 4. All studies enrolled patients with KL 4. In addition, eligible subjects had at least moderate pain at Baseline (defined as a score of at least 1.5 on the WOMAC Index 3.1, 5-point Likert pain subscale at screening) in the study knee, which was to have been symptomatic for greater than 6 months with a clinical diagnosis of OA confirmed by radiological evidence. The clinical effects of treatment on OA pain were evaluated during clinic visits, with phone call follow-ups at intermittent times.

Table 1.5.1
Summary of the Studies Conducted with Ampion™ Administered as an Intra Articular Injection to the Knee

Study	Phase	N	N, KL 2, 3, 4	Route of Administration	Primary outcome	Primary endpoint	Additional outcomes	Test product
Single-Injection Phase 3 Studies in Support of Efficacy & Safety								
AP-003-A	3	329	115 / 139 / 75	Single IA injection	WOMAC A pain, 5-point Likert scale	Week 12	WOMAC B WOMAC C PGA OMERACT-OARSI Rescue analgesia	Ampion, 4 mL or 10ml*
AP-004	3	538	133 / 195/ 210	Single IA injection	WOMAC A pain, 5-point Likert scale	Week 12	WOMAC C PGA WOMAC A pain over 12 weeks	Ampion, 4 mL

Study	Phase	N	N, KL 2, 3, 4	Route of Administration	Primary outcome	Primary endpoint	Additional outcomes	Test product
AP-003-B	3	480	101 / 247 / 132	Single IA injection	WOMAC A pain, 5-point Likert scale	Week 12	WOMAC B WOMAC C PGA Rescue analgesia WOMAC A pain with movement, pain at rest	Ampion, 4 mL
Additional Clinical Studies in Support of Safety								
AP-007	1 / 2	47	2 / 23/ 15	Multiple IA injection; 3 injections, every 2 weeks	WOMAC A pain, 5-point Likert scale	Week 20	WOMAC B WOMAC C PGA Physical activity Radiologic changes	Ampion, 4 mL
AP-008	3	342	0 / 114 / 228	Multiple IA injection; 3 injections, every 2 weeks	WOMAC A pain, 5-point Likert scale	Week 20	WOMAC B WOMAC C PGA Physical activity WOMAC A pain with movement	Ampion, 4 mL
AIK	1 / 2	103	33 / 69 / 1	Single IA injection	Pain, 10-point NRS	Day 3, 8, 30 and 84	WOMAC total, parts A, B, C Range in motion Rescue analgesia	Ampion 10 ml, alone or in solution with betamethasone and/or lidocaine and/or saline
Total		1839						

*Both doses of Ampion, 4 mL and 10 mL, are safe, efficacious and well tolerated. In the absence of a difference in efficacy for the 4 mL and 10 mL Ampion doses, the lower dose of 4 mL will be used for subsequent phase 3 studies.

In all three well-controlled, single-injection studies, Ampion demonstrated a numerically greater effect in the KL 4 patients compared to saline, indicating a reproducible and consistent response. Analysis of the combined data demonstrate a statistically significant

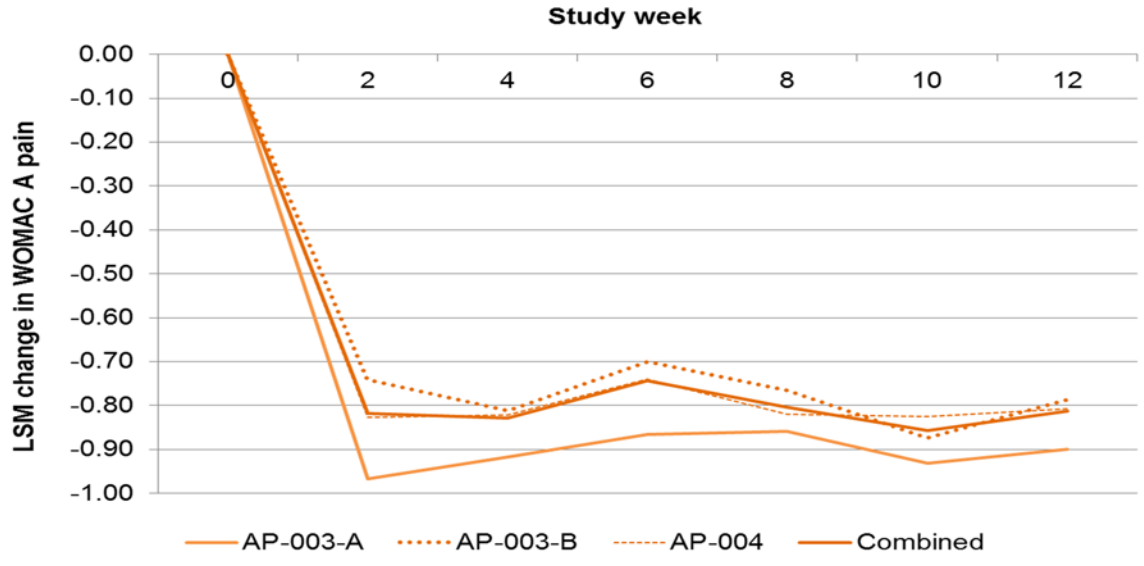
result in this underserved patient population. Table 1.5.2 presents the data for KL 4 patients from all single-injection studies, analyzed according to the SAP for the respective study.

Table 1.5.2
Descriptive Statistics and Analysis Results for KL 4 Subjects for Each Study and All Studies Combined

Study ID	Parameter	Saline	Ampion	Unadjusted Diff. (Ampion-Saline)	LS Adjusted Diff. (Ampion-Saline)
Combined	N	223	194		
	Mean	-0.62	-0.82	-0.21	-0.19
	Std. Dev.	0.883	0.817		
	p-value			**0.0125**	**0.0155**
AP-003-A	N	43	32		
	Mean	-0.51	-0.86	-0.35	-0.42
	Std. Dev.	0.906	0.772		
	p-value			0.0774	**0.0164**
AP-003-B	N	67	65		
	Mean	-0.62	-0.81	-0.19	-0.14
	Std. Dev.	0.926	0.842		
	p-value			0.2197	0.3516
AP-004	N	113	97		
	Mean	-0.65	-0.82	-0.17	-0.15
	Std. Dev.	0.851	0.823		
	p-value			0.1440	0.1765

Figure 1 visually represents the consistent reduction in pain for Ampion-treated patients over a 12-week period.

Figure 1.
LS Mean Change for Ampion-Treated Patients Over Time and by Study



In accordance with FDA guidance on osteoarthritis, responder analysis according to the OMERACT-OARSI criteria was applied to previously conducted clinical trials, Table 1.5.3.

Table 1.5.3
Responder analysis in KL 4 patients across single injection studies using OMERACT-OARSI criteria

Study ID	Ampion Responder (%)
AP-003-A	59.4%
AP-003-B	59.7%
AP-004	57.7%
Combined	58.6%

In addition to the efficacy analysis described in this section, Ampion has also demonstrated a robust safety profile across the three well-controlled, single-injection studies, as well as the multiple-injection and early phase trials (Table 1.5.4). No drug-related Serious Adverse Events (SAEs) have been reported in 1,839 patients treated during the clinical development program. The Adverse Event (AE) profile is similar for Ampion and saline, with a majority of the AEs of minor or moderate severity and unrelated to treatment.

Table 1.5.4
Summary of Treatment-Emergent Adverse Events

Treatment emergent AE	Saline	Ampion
Overall	N=907	N=932
One or more TEAE	425 (47%)	421 (45%)
One or more related TEAE	63 (7%)	73 (8%)
KL grade 4	N=338	N=326
One or more TEAE	150 (44%)	145 (44%)
One or more related TEAE	20 (6%)	24 (7%)

CONCLUSIONS

Clinical efficacy observed in previous single-injection studies suggest that Ampion safely relieves pain due to severe, KL 4, osteoarthritis of the knee, the most severe form of OAK, for which there is no FDA approved treatment alternative. While opioids can treat pain, and total knee replacement can excise the affected tissues, the ability to treat OAK pain and inflammation locally is an unmet medical need. Currently, when KL 4 patients are treated for OAK, they are receiving treatment using intra-articular therapy (such as viscosupplementation) that were not studied, nor required in their device approvals to demonstrate efficacy in the KL 4 population (Rutjes 2012). Without surgery, with only a single intra-articular injection of Ampion, KL 4 patients are able to achieve clinically meaningful pain relief.

2 RATIONALE FOR THE STUDY

This is a phase 3 randomized study is to confirm the efficacy of an intra-articular injection of Ampion™ and is designed to follow on from the completed single-injection Ampion studies. This study explores the clinical impact of Ampion-treatment in patients with severe OA using criteria developed by OMERACT-OARSI (Pham 2004).

The appropriateness of a within-patient multi-component endpoint is generally determined by clinical considerations, and as such, the OMERACT-OARSI responder criteria, which evaluates pain, function and patient global assessment, and has been deemed clinically meaningful for OA trials, remains an endpoint in this clinical investigation.

In addition to evaluating response to treatment (Y/N), the study will evaluate a composite endpoint of pain and function, as well as improvement in PGA, using OMERACT-OARSI criteria. Analysis of Ampion response to saline from previously conducted single-injection Ampion studies will also be evaluated.

Ampio plans to evaluate patients who complete study AP-003-C in an open label extension study. The protocol for the open-label extension study will be submitted under separate cover.

2.1 RATIONALE FOR THE DOSES AND THE DOSING REGIMEN

This trial will use the 4 mL volume of Ampion used in the single-injection studies (AP- 003-A, AP-004, and AP-003-B).

3 STUDY DESIGN

3.1 STUDY DESIGN OVERVIEW

A confirmatory, randomized, phase 3 study with a 7-day screening period for each subject followed by a 12-week participation period. A total of 171 subjects with knee pain and decreased function due to severe osteoarthritis (KL 4) will be enrolled in a 6:1 randomization schema: 4 mL Ampion intra-articular injection: 4 mL saline intra-articular injection. Study visits will include: Screening visit, Baseline, a 24-hour, a post- injection follow-up phone call, Week 2 phone visit, Week 6, Week 10 phone visit, and Week 12 for a total of 7 visits. Screening, Baseline, Week 6 and Week 12 are in-office visits.

The clinical effects of Ampion treatment on OA pain will be evaluated during in-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®) and the Patient's Global Assessment of disease severity (PGA).

The WOMAC® is a validated Osteoarthritis 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 scale and PGA will be asked of subjects.

Clinical benefit will be established by evaluation of the OMERACT-OARSI response using the WOMAC and PGA scales as assessed during the in-office visits and phone visits. Safety will be assessed by recording adverse events (post-injection and at all follow-up contacts), physical examinations, vitals (Baseline, Weeks 6 and 12), and laboratory analysis (Screening and Week 12).

3.2 STUDY OBJECTIVES

3.2.1 Primary Objective

The primary trial objective is to evaluate the clinical efficacy of a single intra-articular injection (4 mL) of Ampion.

3.2.2 Secondary Objective

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

3.3 SAFETY MONITORING COMTTEE

A Safety Monitoring Committee (SMC) will be established to review the safety of Ampion as the study progresses. The SMC will consist of independent clinicians not involved in the clinical trial. The SMC will be primarily responsible for reviewing any serious Adverse Event (SAE) and other clinically important safety findings (e.g., discontinuations due to

AEs) that may occur during the study. A charter will be developed to detail the SMC review responsibilities, the frequency of meetings, and data evaluation plans.

3.4 STOPPING RULES

The entire study may be stopped under defined circumstances as outlined in Section 7.

3.5 STUDY ENDPOINTS

3.5.1 Primary Endpoint

- Evaluate improvement of OMERACT-OARSI response of a single 4 mL Ampion intra-articular injection from Baseline to Week 12

3.5.2 Secondary Endpoint

- Evaluate improvement in the composite endpoint of pain and function (WOMAC A and C) from Baseline to Week 12
- Evaluate improvement in PGA from Baseline to Week 12
- Evaluate improvement in the composite endpoint of pain and function (WOMAC A and C) compared to saline from all single-injection Ampion studies

3.5.3 Exploratory Endpoint

- N/A

3.6 BLINDING AND RANDOMIZATION

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

A comprehensive presentation of the data management and statistical analysis plan will be approved by Ampio Pharmaceuticals, Inc. prior to final analysis of study data.

4 SELECTION OF SUBJECTS

4.1 NUMBER OF SUBJECTS

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).

4.2 RECRUITMENT METHODS

Subjects will be recruited from the population being seen by Investigators at the clinical sites participating in the study. In addition, notifications about the opportunity for subjects to participate in a clinical trial will be sent to referring physicians. A description of the clinical trial will also be posted at ClinicalTrials.gov, and advertisements and/or other notices may be produced to advise potential study subjects on how they may obtain information about study participation. All such materials will be reviewed and approved by the Institutional Review Board (IRB) prior to their publication or dissemination.

4.3 INCLUSION CRITERIA

Subjects should fulfill all of the following inclusion criteria:

1. Able to provide written informed consent to participate in the study;
2. Willing and able to comply with all study requirements and instructions of the site study staff;
3. Male or female, 40 years to 85 years old (inclusive);
4. Must be ambulatory;
5. Study knee must have a clinical diagnosis of OA supported by radiological evidence (Kellgren Lawrence Grade 4) which is assessed locally (x-rays within the past 6 months of screening are acceptable);
6. Moderate to moderately-severe OA pain in the study knee (rating of at least 1.5 on the WOMAC A, 5-point Likert Pain Subscale);
7. Moderate to moderately-severe OA function in the study knee (rating of at least 1.5 on the WOMAC C, 5-point Likert Function Subscale);
8. WOMAC A, 5-point Likert pain subscale <1.5 in the contralateral knee,;
9. Ability to discontinue NSAID use at Screening visit and/or 72 hours prior to the Baseline visit and for the duration of the clinical study (low-dose Aspirin (81 mg) is allowed during the study);
10. No analgesia (including acetaminophen) taken 24 hours prior to an efficacy measure;
11. No known clinically significant liver abnormality (e.g. cirrhosis, transplant, etc.).

4.4 EXCLUSION CRITERIA

Subjects fulfilling one or more of the following criteria may not be enrolled in the study:

1. As a result of medical review and screening investigation, the Principal Investigator considers the subject unfit for the study
2. A history of allergic reactions to human albumin (reaction to non-human albumin such as egg albumin is not an exclusion criterion)
3. A history of allergic reactions to excipients in 5% human albumin (N-acetyltryptophan, sodium caprylate)
4. Presence of tense effusions
5. Inflammatory or crystal arthropathies, acute fractures, history of aseptic necrosis or joint replacement in the affected knee, as assessed locally by the Principal Investigator
6. Isolated patella femoral syndrome, also known as chondromalacia
7. Any other disease or condition interfering with the free use and evaluation of the study knee for the duration of the trial (e.g. cancer, congenital defects, spine osteoarthritis)
8. Major injury to the study knee within the 12 months prior to screening
9. Severe hip osteoarthritis ipsilateral to the study knee
10. Any pain that could interfere with the assessment of study knee pain (e.g. pain in any other part of the lower extremities, pain radiating to the knee)
11. Any pharmacological or non-pharmacological treatment targeting OA started or changed during the 4 weeks prior to randomization or likely to be changed during the duration of the study
12. Pregnancy or planning to become pregnant during the study
13. Use of the following medications:
    a. No IA injected medications in the study knee during the study (or 12 weeks prior to Baseline).
    b. No analgesics containing opioids.
    c. NSAIDs are not permitted during the study; acetaminophen is available as a rescue medication during the study from the provided supply.
    d. No topical treatment on the study knee during the study
    e. No significant anticoagulant therapy (e.g. Heparin or Lovenox) during the study (treatment such as low-dose Aspirin (81 mg) and Plavix are allowed)
    f. No systemic treatments that may interfere with safety or efficacy assessments during the study
    g. No immunosuppressants
    h. No use of systemic or intra-articular corticosteroids
14. No human albumin treatment in the 3 months before randomization or throughout the duration of the study

4.5 INCLUSION OF SUBJECTS INCAPABLE OF GIVING INFORMED CONSENT

No subject incapable of giving informed consent may be enrolled in the study.

5 STUDY PLAN AND PROCEDURES

Subjects will be randomized into the study 6:1 to receive an IA injection of 4 mL Ampion™ or 4 mL saline on Visit 2, Day 0 (Baseline). Telephone contact will be made with the subject 24 hours after the IA injection. The subject will be followed for 12 weeks and the clinical effects of treatment on OA pain will be evaluated during clinic visits at 6 and 12 weeks, and during telephone contacts at 2 and 10 weeks, using the WOMAC osteoarthritis Index 3.1 (pain subscore, stiffness subscore and function subscore) and an overall global severity assessment (Patient's Global Assessment [PGA]). Safety will be assessed by recording adverse events (through 24 hours post-dose and at all follow up in-clinic visits and telephone contacts), vital signs (Baseline, and Weeks 6 and 12), recording prior and concomitant medications including start/stop dates, indication, dose and frequency (through 24 hours post-dose and at all follow up in-clinic visits and telephone contacts), physical examination (Baseline and Weeks 6 and 12), and laboratory tests (Screening and Week 12). The assessments and procedures performed at each subject visit or contact are described in Section 5.1 and in Table 6.1.

5.1 DESCRIPTION OF STUDY VISITS

5.1.1 Visit 1 (Day -7 through Day 0, in-clinic); Screening

The following procedures will be performed at Visit 1 (Screening):

- Obtain written informed consent before the start of any study specific procedure.
- Review medical history including all previous treatments for OA.
- Record prior and concomitant medications including start/stop dates, indication, dose and frequency.
- Record demographic data including date of birth, gender and race.
- Measure and record height and weight.
- Perform and record physical examination.
- Record WOMAC Index 3.1, 5-point Likert scale (sections A-C) for the study knee
- Record WOMAC Index 3.1, 5-point Likert scale (section A only) for the contralateral knee
- Record PGA
- Record vital signs. (Measure body temperature, systolic / diastolic blood pressure [BP] and pulse rate).
- Evaluate all inclusion and exclusion criteria to ensure that subjects meet all inclusion criteria and none of the exclusion criteria. If subject meets all inclusion/exclusion criteria up to this point, move forward with x- ray and laboratory assessments.
- Obtain x-ray of study knee and evaluate for KL grade (x-rays within 6 months of the screening date are acceptable)
- Collect blood sample for local laboratory assessment.
- Collect urine hCG in women of child-bearing potential. Evaluate for pregnancy.

5.1.2 Visit 2 (Day 0, in-clinic) Baseline/Randomization/Treatment

The following procedures will be performed at Visit 2 (Baseline/Randomization/Treatment):

- Confirm eligibility by assessing all inclusion/exclusion criteria from the screening visit again at Baseline. Confirm KL grade from Principal Investigator.
- Perform WOMAC (sections A-C), using the 5-point Likert scale for the evaluation of the study knee. Confirm Baseline WOMAC Pain (WOMAC A) and WOMAC Function (WOMAC C) meet Inclusion #6 and #7 prior to enrollment.
- Perform PGA evaluation of the study knee.
- Record concomitant medications.
- Perform and record physical examination.
- Record vital signs. (Measure body temperature, systolic / diastolic blood pressure [BP] and pulse rate) pre- and post-injection.
- If subject meets all inclusion/exclusion, subject can be enrolled into study
- Perform intra-articular injection of study drug.
- Record post-injection AEs if observed.
- Issue rescue medication (acetaminophen).

5.1.3 Visit 3 (Day 1, telephone contact)

The following procedures will be performed at Visit 3:

- Record AEs.
- Record concomitant medications.
- Review rescue medication use.

5.1.4 Visit 4 (Week 2 ± 7 days, telephone contact)

The following procedures will be performed at Visit 4:

- Perform WOMAC (sections A-C), using the 5-point Likert scale for evaluation of the study knee.
- Perform PGA evaluation of the study knee.
- Record AEs.
- Record concomitant medications.
- Review rescue medication use.

5.1.5 Visit 5 (Week 6 ± 7 days, in-clinic)

The following procedures will be performed at Visit 5:

- Perform and record physical examination.
- Record vital signs. (Measure body temperature, systolic / diastolic blood pressure [BP] and pulse rate).
- Perform WOMAC (sections A-C), using the 5-point Likert scale for the evaluation of the study knee.
- Perform PGA evaluation of the study knee.
- Record AEs.
- Record concomitant medications.
- Review rescue medication use.

5.1.6 Visit 6 (Week 10 ± 7 days, telephone contact)

The following procedures will be performed at Visit 6:

- Perform WOMAC (sections A-C), using the 5-point Likert scale for the evaluation of the study knee.
- Perform PGA evaluation of the study knee.
- Record AEs.
- Record concomitant medications.
- Review rescue medication use.

5.1.7 Visit 7 (Week 12 ± 7 days, in-clinic)

The following procedures will be performed at Visit 7:

- Perform and record physical examination (including weight).
- Record vital signs. (Measure body temperature, systolic / diastolic blood pressure [BP] and pulse rate).
- Perform WOMAC (sections A-C), using the 5-point Likert scale for the evaluation of the study knee.
- Perform PGA evaluation of the study knee.
- Collect blood sample for local laboratory assessment.
- Record AEs.
- Obtain information from subject about medical care for knee OA prior to participation in the current study (medical history).
- Record concomitant medications.
- Review, count, and collect rescue medication.

5.1.8 Early Termination Visit

The following procedures will be performed at Early Termination Visit:

- Perform and record physical examination, including weight.
- Record vital signs. (Measure body temperature, systolic / diastolic blood pressure [BP] and pulse rate).
- Perform WOMAC (sections A-C), using the 5-point Likert scale for the evaluation of the study knee.
- Perform PGA evaluations of the study knee.
- Collect blood sample for laboratory assessment.
- Record AEs.
- Obtain information from subject about medical care for knee OA prior to participation in the current study (medical history).
- Record concomitant medications.
- Review, count, and collect rescue medication.

5.1.9 Unscheduled Visits

Additional visits may be scheduled at the discretion of the Investigator, for example as part of follow up of AEs. Unscheduled Visits, if patient is terminated from the study, should follow the visit structure described for the Early Termination visit. All unscheduled visits should include review of potential AEs.

5.1.10 Missed Visits

Subjects unable to complete a study visit as scheduled should be re-scheduled for a replacement visit as soon as possible. If a subject misses any scheduled follow up visit and cannot be seen prior to the start of the visit range for the next visit, the visit is considered missed.

5.1.11 CONCOMITANT MEDICATIONS AND RESCUE MEDICATION

The following medications/therapies are NOT allowed during this clinical study:

1. No IA injected medications in the study knee during the study.
2. No analgesics containing opioids.
3. NSAIDs may not be used during the study (low-dose Aspirin (81 mg) is allowed). Acetaminophen is available as a rescue medication during the study from the provided supply.
4. No non-pharmacological treatment targeting OA started or changed during the study.
5. No topical treatment on the study knee during the study.
6. No significant anticoagulant therapy (e.g. Heparin or Lovenox) during the study (treatment such as low-dose Aspirin (81 mg) or Plavix is allowed)
7. No systemic treatments that may interfere with safety or efficacy assessments during the study.
8. No immunosuppressants.
9. No use of systemic or intra-articular corticosteroids
10. No human albumin treatment during the study.

Any medication used during the study should be recorded. All concomitant medication start and stop dates, total daily dose, route and indication should to be recorded.

The only allowed analgesia medication during the 12-week study is 500 mg of acetaminophen, 1 tablet every 4 hours as required by the subject, not to exceed 3,000 mg of acetaminophen in a 24-hour period. Dose must be reduced if using other medications that contain acetaminophen (cold medicines, etc.).

6 METHODS OF ASSESSMENT

Demographic Data

At Visit 1 (Screening), subject demographic data will be collected. These include: date of birth, gender and race.

Medical History

At Visit 1 (Screening) a complete medical history, including prior interventions to the study knee, will be obtained from each subject.

Concomitant Medications

Detailed history of medications will be documented for each subject at Visit 1 (Screening) and Visit 2 (Baseline). Concomitant medications (especially any changes in medication) will be documented for each subject at each scheduled visit.

Kellgren-Lawrence Grading Scale

Radiographic images should be evaluated according to the Kellgren-Lawrence Grading Scale as noted below in Figure 2.

FIGURE 2: Kellgren-Lawrence Grading System

Grade	Description
0	Normal knee without osteophytes or joint space narrowing
1	Possible osteophytic lipping and doubtful narrowing of joint space
2	Definite osteophytes and possible narrowing of joint space
3	Moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends
4	Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends

Physical Examination and Vital Signs

Height in feet and inches will be measured at Visit 1 (Screening).

Body weight in pounds (lb) will be measured at Visit 1 (Screening) and at Visit 7 (Week 12 or Early Termination Visit).

Body temperature (deg F) will be measured at each visit.

Systolic and diastolic BP and pulse rate will be measured with the subject in a seated position.

The full physical examination will consist of examining the following body systems: cardiovascular, respiratory, abdominal, skin and musculoskeletal other than the knee. The

physical examination of the target knee will consist of evaluating the knee joint for effusion and tenderness on palpation.

Laboratory Assessments
Blood will be collected at Screening and Week 12 and analyzed by a local lab. Reference ranges must be available to evaluate lab values during the course of the study.

See Table 6.1 for full schedule of assessments and procedures

6.1 EFFICACY ASSESSMENTS

Note: Efficacy questionnaire questions will be asked "with reference to study knee" i.e. to obtain scores specific for the treated knee.

6.1.1 WOMAC® Osteoarthritis Index (Bellamy 1988)

WOMAC Index 3.1 (sections A-C), using the 5-point Likert scale, should be completed by subjects at Screening, pre-dose and pre-aspiration as applicable on Day 0 and at Weeks 2, 6, 10 and 12. All subjects are required to take at least 5 minutes to complete the questionnaire. Subjects are asked about their pain, stiffness, and function in the knee (study joint) due to arthritis during the last 24 hours.

Subjects respond to each subscale by using a 5-point Likert score (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme).

6.1.2 Patient's Global Assessment of Disease Severity (PGA)

The PGA should be completed by subjects at Screening, pre-dose and pre-aspiration as applicable on Day 0 (prior to injection), and at Weeks 2, 6, 10 and 12.

Subjects are asked the following question: "Considering all the ways in which your arthritis affects you, please indicate how you are doing."

Subjects respond by using a 5-point adjectival Likert score (0 = very well, 1 = well, 2 = fair, 3 = poor, 4 = very poor).

6.2 SAFETY PARAMETERS

Based on results of previous studies of a single intra-articular injection of Ampion™ < 5 kDa ultrafiltrate of 5% HSA in adults with OA of the knee in which no clinically significant differences between active and saline were found, safety will be assessed by recording adverse events, vital signs, results of physical examination, recording prior and concomitant medications and safety labs.

6.2.1 Vital Signs

Vital signs (radial pulse rate, blood pressure, and body temperature) should be recorded at Screening, pre- and post–treatment on Day 0, and then on visits at Weeks 6 and 12.

Vital signs should be taken after the subject has rested in a seated position for at least 5 minutes.

6.2.2 Clinical laboratory tests

Subjects in the will undergo a blood draw at Screening and Week 12. Blood draws should be done after subject meets all other inclusion/exclusion criteria at Screening; Blood draws should be done at Week 12 after all WOMAC and PGA assessments are completed. All clinically significant values will be followed up at the Investigator's discretion. Blood laboratory results must be reviewed and compared to reference ranges throughout the study to evaluate for potential adverse events. Blood draws will be performed in compliance with standard laboratory procedures.

The following analysis will be conducted by the local laboratory:

Serum biochemistry: Sodium, potassium, chloride, bicarbonate, glucose, urea, creatinine, creatine kinase, urate, phosphate, total calcium, cholesterol, albumin, globulins, protein, total bilirubin, conjugated bilirubin, gamma glutamyltransferase (GGT), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LD).

Hematology: Hemoglobin, red blood cell count, hematocrit, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), platelets, white cell count, neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

In addition to the tests stated above, all female subjects with child-bearing potential will be tested for serum hCG (for exclusion #12/pregnancy).

TABLE 6.1 SCHEDULE OF ASSESSMENTS AND PROCEDURES

	Screening VISIT 1	Baseline Randomization Treatment VISIT 2	Post-treatment check (telephone contact) VISIT 3	Week 2 (telephone contact) VISIT 4	Week 6 VISIT 5	Week 10 (telephone contact) VISIT 6	Week 12 Final Visit VISIT 7	Early Termination
Visit # Day	**1 Day-7 to 0**	**2 Day 0**	**3 Day 1**	**4 Day 14 ± 7**	**5 Day 42 ± 7**	**6 Day 70 ±7**	**7 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 A-C, 5-point Likert Scale	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	X
Treatment with study drug		X						
Rescue medication dispensed/collected		X					X	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 #5. X-rays obtained within 6 months of screening are acceptable.

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

*Includes height and weight at Screening (Visit 1) and Week 12 (Visit 7)

7 DISCONTINUATION CRITERIA

7.1 EARLY DISCONTINUATION OF THE STUDY

It is agreed that for reasonable cause, either the investigator or the Sponsor may terminate this study, provided a written notice is submitted at a reasonable time in advance of intended termination; if by the investigator notice is to be submitted to Ampio Pharmaceuticals, Inc., and if by the Sponsor, notice will be provided to each investigator.

If a severe local reaction or drug-related SAE occurs at any time during the study, the Safety Monitoring Committee will review the case immediately.

The study will be immediately suspended and no additional Ampion treatments administered pending review and discussion of all appropriate study data by the SMC if 1 or more subjects develop any of the following adverse events deemed to be possibly, probably, or definitely related to Ampion by the Investigator and/or Medical Monitor, based upon close temporal relationship or other factors:

- Death
- Anaphylaxis (angioedema, hypotension, shock, bronchospasm, hypoxia, or respiratory distress)
- Induction of autoimmune arthritis
- Hepatic failure
- Aplastic anemia.

The study will not be restarted until all parties have agreed to the course of action to be taken and the IRB/EC has been notified.

7.2 EARLY DISCONTINUATION OF INDIVIDUAL SUBJECTS

Subjects are to be withdrawn from the study for any of the following reasons:

- Withdrawal of informed consent
- Subject is lost to follow up.

Subjects will also be withdrawn at any time if the investigator concludes that it would be in the subject's best interest for any reason. Protocol violations do not lead to subject withdrawal unless they constitute a significant risk to the subject's safety.

Subjects can voluntarily withdraw from the trial for any reason at any time. They are to be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow up for any reason. Subjects withdrawing from the study because of an AE should be followed for at least 30 days, resolution of the AE or until no further improvement is expected, whichever comes first.

8 TREATMENT

Eligible subjects will be randomized (6:1) to a single 4 mL Ampion intra-articular injection or a single 4 mL saline injection into the study knee.

Subjects will be randomized to an assigned subject number after confirmation of eligibility, just prior to treatment.

8.1 DOSING AND ADMINISTRATION OF STUDY MEDICATION

Appropriately trained site personnel should administer the study treatment.

If both knees are osteoarthritic, then at Screening the Investigator should select the knee that best satisfies the requirements for the study (see inclusion criteria 6 - 7) as the study knee. At the time of dose administration, the study knee should be treated with received investigational product in accordance with the randomization schedule. The other knee should receive standard of care.

Aspiration of the study knee should only occur if an effusion is present. Aspiration and volume of aspiration should be noted on the study source notes/eCRF. The study treatment should be administered as an injection into the knee joint space under sterile prep conditions, (i.e. prior to injection, the knee should be cleaned with an antiseptic).

The recommended procedures is to administer the injection into the knee joint space with the subject in the seated position with the treatment knee flexed at 90°. The area of injection is inferior lateral to the patella; lateral level of the joint line.

The Principal Investigator may determine whether anesthesia of the treatment area with a topical anesthesia or nothing is appropriate. Injection of lidocaine prior to the Ampion injection is not allowed.

The needle should be passed through the fat pad to the firm surface of the intercondylar notch. Following the withdrawal of the needle, it is recommended that fingertip pressure be applied to the injection site, and then a sterile dressing (BandAid) is used to cover the injection site. Injection should proceed easily.

The recommended needle for this injection is a 25-gauge needle that is 1.5 inches long.

Failure to easily inject should be documented as a potential non-inter-articular injection. The injector and date of administration should be recorded in the study source notes/eCRF.

Subjects should be advised to abstain from submersing their knee in water for at least 24 hours (swimming pool, baths, lakes, ect.). Showering is acceptable.

8.2 DRUG STORAGE AND ACCOUNTABILITY

Study drug should be stored at room temperature (59º – 77ºF or 15º – 25ºC) in a secure area with restricted access and temperature monitoring. A temperature monitor calibration must be provided to the CRO prior to receiving study drug.

The Investigator, the clinical site staff, or other personnel authorized to store and dispense investigational product is responsible for ensuring that the investigational product used in the clinical study is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

All investigational product is to be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record is maintained of investigational product issued and returned.

If any quality issue is noticed upon the receipt or use of an investigational product (i.e. deficiencies in condition, packaging, appearance, associated documentation, labeling, expiry date, temperature, etc.), Ampio Pharmaceuticals, Inc. must be promptly notified. Temperature monitors, and instructions to download the temperature data to Ampio Pharmaceuticals, Inc., will be included with each site shipment of study drug.

Under no circumstances may the Investigator supply investigational product to a third party, allow the investigational product to be used other than as directed by this clinical study protocol, or dispose of investigational product in any other manner.

All investigational product, used or unused during the study, must be retained in the study kit until notification from Ampio or designated representative. Ampio, or designated representative will instruct sites on study drug returns and/or destruction of study drug.

8.3 TREATMENT COMPLIANCE

The injection of study drug will be performed by the Investigator or a designated member of the site clinical staff. A 5mL syringe, a 25-gauge needle, and a bottle of rescue medication will be included in every subject kit.

During monitoring visits, monitors will visually inspect each vial to ensure full injection volume was used. Compliance with treatment is thus assured.

9 ADVERSE EVENTS

9.1 DEFINITION OF AN ADVERSE EVENT

An adverse event (AE) is defined as any undesired medical occurrence in a subject or clinical investigation subject 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), symptom, or disease temporarily associated with the use of a study drug, whether or not related to the study drug.

Assessment of severity of an AE will be rated according to categories listed in TABLE 9.1.

TABLE 9.1 DEFINITIONS OF AE SEVERITY

Grade 1 (MILD): The symptom is barely noticeable to the study subject 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 subject 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 subject 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.

Determination of the relationship between the AE and the study drug will be made using the guidelines presented in TABLE 9.2.

TABLE 9.2 GUIDELINES FOR DETERMINING THE RELATIONSHIP (IF ANY) BETWEEN ADVERSE EVENT AND THE STUDY DRUG

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.

9.2 DEFINITION OF A SERIOUS ADVERSE EVENT

A Serious Adverse Event (SAE) is any untoward medical occurrence that occurs at any dose that:

- Results in death
- Is life-threatening (subject 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

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Hospitalizations for elective surgery or other medical procedures that are not related to a treatment-emergent AE are not considered SAEs.

9.3 RECORDING OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Recording and reporting of adverse events should be in accordance with the FDA final "Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies" of December 2012.

Any AE is to be recorded in the eCRF. In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words. Whenever possible, the investigator should combine signs and symptoms that constitute a single diagnosis.

The existence of an AE may be concluded from a spontaneous report of the subject; from the physical examination; or from special tests e.g., laboratory assessments, where applicable, or other study-specified tests (source of AE).

The reporting period begins from the time that the subject receives IA injection at the Baseline visit through subject's Final Visit at 12 weeks. Any events continuing at study exit will be followed for 30 days or to resolution, or until no improvement is expected, whichever comes first. Any SAE occurring after the reporting period must be promptly reported if a causal relationship to the investigational drug is suspected. If the subject begins a new therapy, the safety reporting period ends at the time the new treatment is started, however, death must always be reported when it occurs during the 12-week study period, irrespective of intervening treatment.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

9.3.1 AE Follow up

All AEs occurring during the study are to be followed up in accordance with good medical practice until they are resolved, stabilized or judged no longer clinically significant or, if a chronic condition, until fully characterized. Any AEs that are considered drug-related (possibly related, definitely related) must be followed for 30 days, or to resolution, or until no improvement is expected, whichever occurs first.

9.3.2 Overdose

No information on treatment of overdose of Ampion is currently available. However, it is common medical practice to administer 5% HSA, the sole starting material of Ampion, in multiple infusions until hemorrhage is controlled thereby resulting in higher systemic concentrations of the significant components of Ampion.

In the case of overdose, the subject should be followed as for an AE and appropriate supportive medical treatment instigated.

9.4 SERIOUS ADVERSE EVENT REPORTING

9.4.1 Reporting Requirements

Unexpected serious suspected adverse reactions are subject to expedited reporting to FDA. ALL SAEs must be entered into the eCRF within 24 hours of first knowledge of the event by study personnel. It is important that the investigator provide his/her assessment of relationship to study drug at the time of the initial report. Entry of an SAE into the eCRF triggers an automatic alert to the CRO safety team. The following information must be reported:

- Protocol number
- Site and/or Investigator number
- Subject number
- Demographic data
- Brief description of the event
- Onset date and time
- Resolution date and time, if the event resolved
- Current status, if event not yet resolved
- Any concomitant treatment and medication
- Investigator's assessment of whether the SAE was related to Investigative product or not.

The CRO Safety Associate will contact the site for clarification of data entered onto the eCRF, or to obtain missing information. In the event of questions regarding SAE reporting, the site may contact the appropriate individual as in Section 9.4.2.

9.4.2 SAE Information

Ampio Pharmaceuticals Inc., or their designee CRO, is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to FDA according to 21 CFR 312.32 and the final guidance (2012). All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their Institutional Review Board (IRB) or Ethics committee (EC).

10 STATISTICAL METHODS

10.1 GENERAL CONSIDERATIONS

This section describes the rules and conventions to be used in the presentation and analysis of the data. A comprehensive presentation of the data management and statistical analysis plan will be approved by Ampio Pharmaceuticals, Inc., prior to study completion.

10.1.1 Statistical and Analytical Plan:

This is a randomized, confirmatory study in subjects with severe OA (KL 4) of the knee. Subjects will be followed over a 12-week treatment period to assess the efficacy of Ampion™ on changes in pain, stiffness and function, and patient satisfaction (PGA) and to assess the safety of Ampion™ by monitoring adverse events.

A within-patient, multi-component endpoint, OMERACT-OARSI responder analysis, evaluating pain, function, and PGA, will be used as primary analysis for this study.

The saline group in this study is designed to maintain a blind the study is not powered to make inference about patients receiving saline; therefore, the results from patients receiving saline will be summarized but no comparisons or inferences will be made.

10.2 STATISTICAL OBJECTIVES

The primary statistical objective is to evaluate the efficacy of a single intra-articular injection of Ampion. Efficacy will be evaluated by the percentage of patients who are considered an OMERACT-OARSI responder at 12 weeks after a single 4 mL Ampion™ intra-articular injection at Baseline.

OMERACT-OARSI response is evaluated by:

A patient in this study will be considered a responder for the purpose of efficacy analysis if the following criteria is met.

1) The patient has:

    a. a percent improvement in pain (WOMAC pain) from baseline of ≥50% and an absolute change in pain from baseline of ≥ 1 point; or

    b. a percent improvement in function (WOMAC function) from baseline of ≥50% and an absolute change in function from baseline of ≥1 point.

Meeting one of the above criterion designates the patient as a responder. If the patient does not meet this criterion, then the patient must meet the criterion below to be considered a responder.

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

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

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

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

The second statistical objectives are to:

- Evaluate the improvement in the composite endpoint of pain and function (WOMAC A and WOMAC C) from Baseline to Week 12
- Evaluate the improvement in patient global assessment (PGA) from Baseline to Week 12
- Evaluate improvement in the composite endpoint of pain and function (WOMAC A and C) compared to saline from all single-injection Ampion studies.

The composite endpoint of pain and function (WOMAC A and WOMAC C) will be evaluated using a "controlled" OMERACT-OARSI responder criteria, defined as:

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

Improvement in patient global assessment will also follow OARSI's recommendation for a clinically meaningful improvement, defined as:

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

10.3 ANALYSIS POPULATIONS

10.3.1 Safety Analysis Population:

The safety analysis population is defined as all subjects who receive study medication (Ampion or saline). Subjects will be analyzed as treated.

10.3.2 Intent-to-treat Population:

The intent-to-treat (ITT) analysis population is defined as all subjects who are randomized, regardless of whether or not they have received the investigational product, or have a post-baseline visit. All efficacy analyses will be performed in the ITT population. Subjects will be analyzed as treated.

10.3.3 Per Protocol Population:

The per protocol analysis population is defined as all subjects included in the ITT analysis who met all entry criteria, completed the Week 12 visit, and had no major protocol violations. All efficacy analyses will be repeated in the per-protocol population. These analyses will be supportive of the ITT analysis. Subjects will be analyzed as treated.

10.3.4 Hypotheses Tested

For the primary endpoint of the proportion of patients who are responders according to the OMERACT-OARSI criteria, the following hypothesis will be tested.

$H_0: \pi \leq \pi_0$ versus $H_A: \pi > \pi_0$

Where π_0 is the hypothesized 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.

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%.

The secondary endpoints are represented by the proportion of patients who are responders as identified by the following response criteria:

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

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

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

The hypotheses for the first two secondary endpoints are identical and are:

$H_0: \pi \leq 30\%$ versus $H_A: \pi > 30\%$

These will be tested using the exact binomial test.

The hypothesis for the third secondary endpoint will be tested as:

$H_0: \pi_A \leq \pi_{HS}$ 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.

10.3.5 Exploratory Endpoints

None

10.3.6 Definition of Study Visits

This clinical trial has a total of 7 study visits, including telephone contacts, 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.

10.3.7 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).

Since the sample size for adequate power of the primary and second secondary hypotheses is almost identical given the anticipated results of previous studies, the sample size for this study is based on the following hypothesis.

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

A sample size of 146 patients yields a greater than 90% power of rejecting the null hypothesis when the anticipated proportion under the alternative hypothesis is 45%.

10.3.8 Disposition of subjects

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

10.3.9 Interim analysis

There will be no interim analysis.

10.3.10 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.

A comprehensive presentation of the data management and statistical analysis plan will be approved by Ampio Pharmaceuticals, Inc. prior to final analysis to adjust for any changes to the protocol or unexpected issues in the study conduct and data that affect the planned analysis.

10.3.11 Data presentation

10.3.11.1 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) summarized using descriptive statistics, overall and by treatment group for the ITT analysis population.

10.3.11.2 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.

10.3.11.3 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.

10.3.11.4 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.

10.4 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 endpoint (WOMAC A, WOMAC C, and PGA), missing Week 12 values will be imputed when the ITT analysis population is used. 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 used.

11 REGULATORY, ETHICAL AND LEGAL OBLIGATIONS

11.1 DECLARATION OF HELSINKI

The Principal Investigator will ensure that this Study is conducted in accordance with the most recent revision of the Declaration of Helsinki.

11.2 GOOD CLINICAL PRACTICE

The Study will be conducted according to the study protocol and to Standard Operating Procedures (SOPs) that meet the guidelines provided by the International Conference on Harmonisation (ICH) for Good Clinical Practice in clinical studies.

11.3 INSTITUTIONAL REVIEW BOARDS/ETHICS COMMITTEES

Before implementing this study, the protocol, the proposed subject informed consent forms and other information for the subjects, must be reviewed by a properly constituted committee or committees responsible for approving clinical studies. The IRB/IEC written, signed approval letter/form must contain approval of the designated investigator, the protocol (identifying protocol title, date and version number), and of the subject informed consent form (date, version).

Any change or addition to the protocol can only be made in a written protocol amendment, which must be approved by the Sponsor, the IRB/IEC and the Health Authorities.

11.4 REGULATORY AUTHORITY APPROVAL

Before this study is implemented, the protocol must be approved by the relevant regulatory authority.

11.5 INFORMED CONSENT

The investigator must fully inform the subject of all pertinent aspects of the trial including the written information approved/favorably assessed by the IRB/IEC.

Prior to the start of the pre-study examination, the written informed consent form must be signed and personally dated by the subject and by the physician who conducted the informed consent discussion. One copy of the written information and signed consent form must be given to each subject and 1 copy must be retained in the investigator's study records.

11.6 SUBJECT CONFIDENTIALITY AND DISCLOSURE

Data on subjects collected on eCRFs during the trial will be documented in an anonymous fashion and the subject will only be identified by the subject number, and by his/her initials If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, all parties are bound to keep this information confidential.

The investigator will guarantee that all persons involved will respect the confidentiality of any information concerning the trial subjects. All parties involved in the study will maintain strict confidentiality to assure that neither the person nor the family privacy of a subject participating in the trial is violated. Likewise, the appropriate measures shall be taken to prevent access of non-authorized persons to the trial data.

11.7 COLLECTION, MONITORING AND AUDITING STUDY DOCUMENTATION, AND DATA STORAGE

11.7.1 Collection of Data and Monitoring Procedures

This study will use a 21 CFR Part 11 compliant electronic data capture system (eDC). An electronic case report form (eCRF) is used for data recording. All data requested on the eCRF must be entered and all missing data must be accounted for.

The data will be checked for completeness and correctness as it is entered by the real-time online checks applied by the eDC system. Off-line checks will also be run to perform any additional data review required. Discrepancy reports will be generated accordingly and transferred to the study center for resolution by the investigator or his/her designee.

Accurate and reliable data collection will be assured by verification and cross–check of the eCRF against the investigator's records by the study monitor (source document verification), and the maintenance of a study drug–dispensing log by the investigator.

Before study initiation, at a site initiation visit or at an investigator's meeting, a Sponsor representative will review the protocol and case report forms with the investigators and their staff. During the study a monitor will visit the site regularly to check the completeness of subject records, the accuracy of entries on the case report forms, the adherence to the protocol and to Good Clinical Practice and the progress of enrollment. The monitor will ensure during on-site visits that study medication is being stored, dispensed and accounted for according to specifications. Key trial personnel must be available to assist the monitors during these visits.

The investigator must give the monitor access to relevant hospital or clinical records, to confirm their consistency with the case report form entries. No information in these records about the identity of the subjects will leave the study center. Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

11.7.2 Auditing Procedure

In addition to the routine monitoring procedures the Sponsor or the regulatory authority can conduct an audit or an inspection (during the study or after its completion) to evaluate compliance with the protocol and the principles of Good Clinical Practice.

The investigator agrees that representatives of the Sponsor and Regulatory Authorities will have direct access, both during and after the course of this study, to audit and review all study-relevant medical records.

11.7.3 Retention of Documents

The investigator must maintain source documents for each subject in the study, consisting of all demographic and medical information, including laboratory data, etc., and keep a copy of the signed informed consent form. All information on case report forms must be traceable to these source documents in the subject's file. Data without a written or electronic record will be defined before trial start and will be recorded directly on the case report forms, which will be documented as being the source data.

11.8 DISCLOSURE OF INFORMATION

All information provided to the investigator by Ampio Pharmaceuticals, Inc. or their designee, will be kept strictly confidential. No disclosure shall be made except in accordance with a right of publication granted to the investigator.

No information about this study or its progress will be provided to anyone not involved in the study other than to Ampio Pharmaceuticals, Inc. or its authorized representatives, or in confidence to the IRB, or similar committee, except if required by law.

11.9 DISCONTINUATION OF THE STUDY

It is agreed that, for reasonable cause, either the investigator or Ampio Pharmaceuticals, Inc., may terminate the investigator’s participation in this study after submission of a written notice. Ampio Pharmaceuticals, Inc., may terminate the study at any time upon immediate notice for any reason, including the Sponsor’s belief that discontinuation of the study is necessary for the safety of subjects.

11.10 STUDY REPORT, PUBLICATION POLICY AND ARCHIVING OF STUDY DOCUMENTATION

11.10.1 Study Report and Publication Policy

An ICH-compliant integrated clinical and statistical report will be prepared upon completion of the study and data analysis. The results of the study will be published in a relevant peer-reviewed journal, with authorship status and ranking designated according to the acknowledged contributions of participating investigators, institutions and the Sponsor.

11.10.2 Study Documents

The investigator must maintain source documents for each subject in the study, consisting of all demographic and medical information, questionnaires, including laboratory data, radiology data (as applicable), etc., and keep a copy of the signed informed consent form. All information on the e-case report forms must be traceable to these source documents in the subject's file.

Data without a written or electronic record will be defined before trial start and will be recorded directly on the e-case report forms, which will be documented as being the source data.

11.10.3 Archiving of Documents

Essential documents, as listed below, must be retained by the investigator for as long as needed to comply with national and international regulations. The Sponsor will notify the investigator(s)/institution(s) when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

- IRB/IEC/REB approvals for the study protocol and all amendments
- All source documents and laboratory records
- CRF copies (electronic copies on a CDROM)
- Subjects' informed consent forms (with study number and title of trial)
- FDA form 1572
- Any other pertinent study documents.

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13 APPENDICES

13.1 CONTACT LIST

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