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

STUDY PROTOCOL

STUDY NUMBER: AP-003-C-OLE

NCT 03349645

26 MARCH 2018

CLINICAL STUDY PROTOCOL

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

STUDY NUMBER: AP-003-C-OLE

Drug Development Phase:	Phase 3
Investigational Product:	Ampion™
Indication:	Osteoarthritis of the knee
Sponsor:	Ampio Pharmaceuticals, Inc. 373 Inverness Parkway, Suite 200 Englewood, CO 80112
Date:	Version 3.0 26 March 2018

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

PROTOCOL SIGNATURE PAGE

I have read and understand the contents of this clinical protocol for Study No. AP-003-C-OLE dated 26 March 2018 and agree to meet all obligations of Ampio Pharmaceuticals, Inc. as detailed in all applicable regulations and guidelines.

Signed By:

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

PROTOCOL SYNOPSIS

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

Title of Study:

An Open Label Extension (OLE) study to assess the safety of long-term treatment with a 4-mL intra-articular injection of Ampion ™ in adults with pain due to severe osteoarthritis of the knee

Protocol Number:

AP-003-C-OLE

Study Center(s):

Approximately 14 sites

Indication:

Severe osteoarthritis of the knee (OAK) (Kellgren Lawrence Grade 4, KL 4)

Number of subjects:

Up to 161 subjects

Objectives:

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

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

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Methods:

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

AP-003-C-OLE study will include the following visits:

Visit 9	Enrollment (Day 0 = Day 84 of AP-003-C main study ± 170 days, but not to occur before completion of AP-003-C main study), in-office visit
Visit 10	(24 hours after Visit 9), post injection follow-up telephone call
Visit 11	Week 12 (Day 84 ± 14 days), in-office visit
Visit 12	(24 hours after Visit 11), post injection follow-up telephone call
Visit 13	Week 24 (Day 168 ± 14 days), in-office visit
Visit 14	(24 hours after Visit 13), post injection follow-up telephone call
Visit 15	Week 36 (Day 252 ± 14 days), in-office visit
Visit 16	(24 hours after Visit 15), post injection follow-up telephone call
Visit 17	Week 40 (Day 280 ± 14 days), in-office final visit

The safety of repeat dosing will be evaluated at all visits; in-office visit safety assessments will include vital signs, physical exams, evaluation of AEs, and laboratory analysis (Visit 17, Week 40, visit only) and phone visits will evaluate for AEs.

The clinical effects of treatment on the signs and symptoms of OAK will be evaluated during all in-clinic visits using the Western Ontario and McMaster Universities Arthritis Index (WOMAC®) osteoarthritis Index 3.1, and the Patients's Global Assessment of disease severity (PGA). The WOMAC will also be utilized to assess the contra-lateral knee pain, stiffness, and function at Enrollment and Week 40 (or Early Termination Visit).

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

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WOMAC pain scale will be asked of subjects.

Diagnosis and Main Criteria for Inclusion:

1. Subjects who completed the AP-003-C main study and have not developed any exclusionary criteria
2. Able to provide written informed consent to participate in the study
3. Willing and able to comply with all study requirements and instructions of the site study staff
4. Male or female, 40 years to 85 years old (inclusive), as assessed in the AP-003-C main study
5. Must be ambulatory, as assessed in the AP-003-C main study
6. Study knee must have a clinical diagnosis of OA and supported by radiological evidence (Kellgren Lawrence Grade 4) as assessed in the AP-003-C main study.
7. Moderate to moderately-severe OA pain in the study knee (rating of at least 1.5 on the WOMAC Index 3.1 5-point Likert Pain Subscale), as assessed in the AP-003-C main study
8. Moderate to moderately-severe OA function in the study knee (rating of at least 1.5 on the WOMAC Index 3.1 5-point Likert Function Subscale), as assessed in the AP-003-C main study
9. WOMAC A, 5-point Likert pain subscale <1.5 in the contralateral knee, as assessed in the AP-003-C main study
10. Ability to discontinue NSAID ± 72 hours before/after injections (in-office visits). Low-dose Aspirin (81 mg) is allowed during the study but must not be taken at least 24 hours prior to in-office visits
11. No analgesia (including acetaminophen [paracetamol]) taken 24 hours prior to an efficacy measure

Main Criteria for Exclusion:

1. As a result of medical review and screening investigation, the Principal Investigator considers the subject unfit for the study
2. Known clinically significant liver abnormality (e.g., cirrhosis, transplant, etc.)
3. A history of allergic reactions to human albumin (reaction to non-human albumin such as egg albumin is not an exclusion criterion)
4. A history of allergic reactions to excipients in 5% human albumin (N-acetyltryptophan, sodium caprylate)
5. Presence of tense effusions
6. Inflammatory or crystal arthropathies, acute fractures, history of aseptic necrosis or joint

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replacement in the affected knee
7. Isolated patella femoral syndrome, also known as chondromalacia
8. Any other disease or condition interfering with the free use and evaluation of the index knee for the duration of the trial (e.g. cancer, congenital defects, spine osteoarthritis)
9. Major injury to the index knee within the last 12 months
10. Severe hip osteoarthritis ipsilateral to the index knee
11. 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)
12. Any pharmacological or non-pharmacological treatment targeting OA started or changed 4 weeks prior to entry into the AP-003-C-OLE study, or likely to be changed during the duration of the AP-003-C-OLE study
13. Pregnancy or planning to become pregnant during the study
14. Use of the following medications:
    a. No IA injected pain medications in the study knee during the study. HA and steroid injections in the contralateral knee (non-study knee) are acceptable while on study except ± 14 days of an Ampion injection in the study knee
    b. No analgesics containing opioids
    c. NSAIDs are not permitted ± 72 hours before/after injections at in-office visits; 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 Aspirin 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 corticosteroids
    i. No human albumin treatment in the 3 months prior to the AP-003-C main study or interim period prior to enrollment into the AP-003-C-OLE study. No human albumin treatment throughout the duration of the AP-003-C-OLE study

Test Product, Dose and Mode of Administration:

Ampion™ 4-mL intra-articular injection in the knee

Reference Therapy, Dose and Mode of Administration:

Not applicable

Study Duration:

40 weeks

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Ampio Pharmaceuticals, Inc.	Ampion™	Phase 3
Main Study + Extension Study = 52 weeks		
Criteria for Evaluation: Safety: Adverse events, physical examination, vitals, and blood tests Efficacy: WOMAC osteoarthritis Index 3.1 and PGA		
Statistical Methods: Descriptive Statistics will be utilized for the primary and exploratory endpoints. No formal hypothesis testing will be done.		

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
°C	degrees Celsius
°F	degrees Fahrenheit
µg	microgram
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
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
LDH	lactic dehydrogenase
MCH	mean cell hemoglobin
MCHC	mean cell hemoglobin concentration
MCV	mean cell volume
mg	milligram
mL	milliliter
NA	not applicable
ng	nanogram
NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis

Abbreviation	Definition
OMERACT-OARSI	Outcome Measures in Rheumatology Clinical Trials- Osteoarthritis Research Society International
PGA	patient's global assessment of disease severity
PP	per protocol population
Radius	Distance (in Centimeters) from the center of rotation to the bottom of tube in the rotor
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
TKR	Total Knee Replacement
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. To address this, Ampio proposed a 12-week Main Study (AP-003-C) with a 6:1 randomization to protect the blind and prevent any potential bias associated with an open label assessment. In follow up to the Main Study, Ampio is adding a 40-week add-on, open label study to address the safety of repeat injections for a year. The Open Label Study will also analyze efficacy using the Western Ontario and McMaster Universities Arthritis Index (WOMAC®) osteoarthritis Index 3.1, and the Patient's Global Assessment of disease severity (PGA). This study will analyze response according to these individual criteria as well as responder analysis of OMERACT-OARSI criteria.

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 safety and treatment effect of Ampion in subjects with OAK. The study is 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. Subjects were required to have x-ray findings demonstrating KL grade 2, 3, or 4. All studies enrolled subjects 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
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.

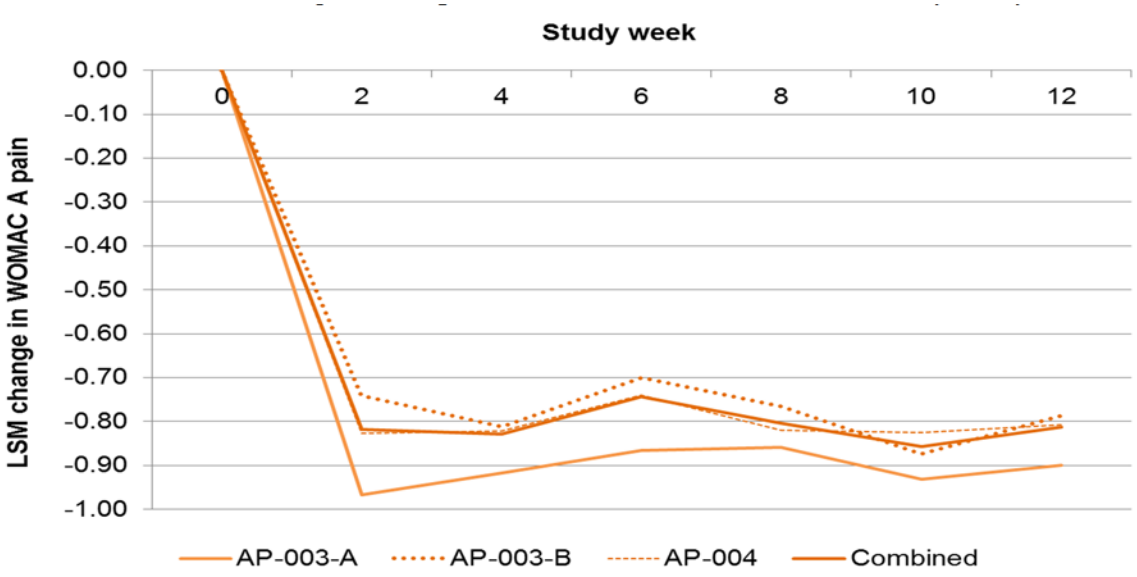
In all three well-controlled, single-injection studies, Ampion demonstrated a numerically greater effect in the KL 4 subjects compared to saline, indicating a reproducible and consistent response. Analysis of the combined data demonstrate a statistically significant result in this underserved patient population. Table 1.5.2 presents the data for KL 4 subjects 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 subjects over a 12-week period.

Figure 1.
LS Mean Change for Ampion-Treated Subjects 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 subjects 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 subjects 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 subjects 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 subjects are able to achieve clinically meaningful pain relief.

2 RATIONALE FOR THE STUDY

This study is designed to follow on from the 12-week AP-003-C main study. This is an open label extension (OLE) to evaluate the safety of repeated dosing of a 4-mL IA injection of Ampion™ every 12 weeks for a total of 52 weeks of study visits.

2.1 RATIONALE FOR THE DOSES AND THE DOSING REGIMEN

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

3 STUDY DESIGN

3.1 STUDY DESIGN OVERVIEW

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

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

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

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

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

3.2 STUDY OBJECTIVES

3.2.1 Primary Objective

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

3.2.2 Exploratory Objectives

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

3.3 SAFETY MONITORING COMMITTEE

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 Medical Monitor and Ampio Pharmaceuticals, Inc. representatives. 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 the incidence and severity of treatment-emergent adverse events (TEAEs)

3.5.2 Exploratory Endpoints

- Responder status based on the OMERACT-OARSI responder criteria
- Evaluate OMERACT-OARSI 'controlled' responder defined as a 20% improvement in Pain and Function and 0.5 point absolute change in the 5-point Likert Scale
- Evaluate 20% improvement in PGA and 0.5 point absolute change in the 5-point Likert Scale
- Mean change and percent change in WOMAC A pain subscore
- Mean change and percent change in WOMAC B stiffness subscore
- Mean change and percent change in WOMAC C physical function subscore
- Mean change and percent change in PGA
- Mean Change and percent change in WOMAC A pain subscore questions 1 and 2 (pain with movement)
- Mean Change and percent change in WOMAC A pain subscore questions 3–5 (resting pain)
- Change in contralateral knee pain (WOMAC A)
- Change in contralateral knee stiffness (WOMAC B)
- Change in contralateral knee function (WOMAC C)
- Time to Total Knee Replacement (TKR)
- Use of rescue analgesia (amount of acetaminophen used)

3.6 BLINDING AND RANDOMIZATION

All subjects will receive Ampion 4-mL which is provided in study kits. Each kit will contain labeled vials, a syringe, a needle and rescue medication.

4 SELECTION OF SUBJECTS

4.1 NUMBER OF SUBJECTS

A total of approximately 161 subjects will be enrolled from the AP-003-C main study into the AP-003-C-OLE study.

4.2 INCLUSION CRITERIA

1. Participation and completion in the AP-003-C study
2. Able to provide written informed consent to participate in the study
3. Willing and able to comply with all study requirements and instructions of the site study staff
4. Male or female, 40 years to 85 years old (inclusive), as assessed in the AP-003-C main study
5. Must be ambulatory, as assessed in the AP-003-C main study
6. Study knee must have a clinical diagnosis of OA and supported by radiological evidence (Kellgren Lawrence Grade 4) as assessed in the AP-003-C main study.
7. Moderate to moderately-severe OA pain in the index knee (rating of at least 1.5 on the WOMAC Index 3.1 5-point Likert Pain Subscale), as assessed in the AP-003-C main study
8. Moderate to moderately-severe OA function in the index knee (rating of at least 1.5 on the WOMAC Index 3.1 5-point Likert Function Subscale), as assessed in the AP-003-C main study
9. WOMAC A, 5-point Likert pain subscale <1.5 in the contralateral knee, as assessed in the AP-003-C main study
10. Ability to discontinue NSAID ±72 hours before/after injections (in-office visits). Low-dose Aspirin (81 mg) is allowed during the study but must not be taken at least 24 hours prior to in-office visits.
11. No analgesia (including acetaminophen [paracetamol]) taken 24 hours prior to an efficacy measure

4.3 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. Known clinically significant liver abnormality (e.g. cirrhosis, transplant, etc.)
3. A history of allergic reactions to human albumin (reaction to non-human albumin such as egg albumin is not an exclusion criterion)
4. A history of allergic reactions to excipients in 5% human albumin (N-acetyltryptophan, sodium caprylate)
5. Presence of tense effusions

6. Inflammatory or crystal arthropathies, acute fractures, history of aseptic necrosis or joint replacement in the affected knee
7. Isolated patella femoral syndrome, also known as chondromalacia
8. Any other disease or condition interfering with the free use and evaluation of the index knee for the duration of the trial (e.g. cancer, congenital defects, spine OA)
9. Major injury to the index knee within the past 12 months
10. Severe hip OA ipsilateral to the index knee
11. Any pain that could interfere with the assessment of index knee pain (e.g. pain in any other part of the lower extremities, pain radiating to the knee)
12. Any pharmacological or non-pharmacological treatment targeting OA started or changed during the 4 weeks prior to enrollment in the OLE study or likely to be changed during the duration of the study
13. Pregnancy or planning to become pregnant during the study
14. Use of the following medications:
    a. No IA injected pain medications in the study knee during the study. HA and steroid injections in the contralateral knee (non-study knee) are acceptable while on study except ± 14 days of an Ampion™ injection in the study knee.
    b. No analgesics containing opioids.
    c. NSAIDs are not permitted ± 72 hours before/after IA injections (in-office visits); 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 Aspirin 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 corticosteroids
    i. No human albumin treatment in the 3 months prior to the AP-003-C main study or interim period prior to enrollment into the OLE study. No human albumin treatment throughout the duration of the OLE study.

4.4 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 receive an IA injection of Ampion™ at Visit 9, Visit 11, Visit 13 and Visit 15 of AP-003-C-OLE. Telephone contact will be made with the subject 24 hours after each IA injection. The subject will be followed until Visit 17. Safety of repeat injections every 12 weeks for 36 weeks will be evaluated during every visit (in-clinic and telephone); in office-visits will evaluate vital signs, physical exam, adverse events, and blood tests (Visit 17 or Early Termination Visit 18 only). Clinical effects of treatment on OA pain will be evaluated during in-clinic visits at Visit 9, Visit 11, Visit 13, Visit 15 and Visit 17 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]). The WOMAC will also be utilized to assess the contralateral knee pain at Visit 9 and Visit 17 (or Early Termination Visit).

The assessments and procedures performed at each subject visit or contact are described in Section 5.1 Description of Study Visits and in Table 6.1, Schedule of Assessments and Procedures.

5.1 DESCRIPTION OF STUDY VISITS

5.1.1 Visit 9 (day -170 to Day 0, in-clinic); Enrollment

The following procedures will be performed at Visit 9 (Day 0):

- Obtain written informed consent for AP-003-C-OLE study before the start of any study specific procedure.
- Review medical history including all previous treatments for OA.
- Evaluate for any AEs ongoing from AP-003-C main study and/or new AEs pre-injection.
- Record prior and concomitant medications including start/stop dates, indication, dose and frequency.
- Record demographic data including year of birth, age, gender and race.
- Measure and record height and weight.
- Obtain hCG urine analysis for women of child-bearing potential
- Perform and record physical examination (prior to injection)
- Record Kellgren Lawrence Grade from radiological assessment, as assessed in AP-003-C main study.
- Complete the WOMAC Index 3.1. for the study knee (prior to injection)
- Complete the WOMAC Index 3.1 for the contralateral knee (prior to injection)
- Complete the PGA for the study knee (prior to injection)
- Evaluate all inclusion and exclusion criteria to ensure that subjects meet all inclusion criteria and none of the exclusion criteria.

- Record vital signs. (Measure body temperature, systolic / diastolic blood pressure [BP] and pulse rate) pre- and post-injection.
- Perform intra-articular injection of study drug.
- Record post-injection AEs if observed.
- Record concomitant medications.
- Issue rescue medication (acetaminophen [paracetamol]).

5.1.2 Visit 10 (24 hours following Visit 9, post-injection follow-up telephone call)

The following procedures will be performed at Visit 10

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

5.1.3 Visit 11 (Day 84 ± 14 days, in-clinic); Week 12

The following procedures will be performed at Visit 11:

- Perform and record physical examination.(prior to injection)
- Record vital signs. (Measure body temperature, systolic / diastolic blood pressure [BP] and pulse rate) pre- and post-injection.
- Complete the WOMAC Index 3.1. for the study knee (prior to injection)
- Complete the PGA for the study knee (prior to injection)
- Perform intra-articular injection of study drug.
- Record post-injection AEs if observed.
- Record concomitant medications.
- Review/Issue rescue medication (acetaminophen [paracetamol]).

5.1.4 Visit 12 (24 hours following Visit 11, post-injection telephone call)

The following procedures will be performed at Visit 12:

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

5.1.5 Visit 13 (Day 168 ± 14 days, in-clinic); Week 24

The following procedures will be performed at Visit 13:

- Perform and record physical examination.(prior to injection)
- Record vital signs. (Measure body temperature, systolic / diastolic blood pressure [BP] and pulse rate) pre- and post-injection.

- Complete the WOMAC Index 3.1. for the study knee (prior to injection)
- Complete the PGA for the study knee (prior to injection)
- Perform intra-articular injection of study drug.
- Record post-injection AEs if observed.
- Record concomitant medications.
- Review/Issue rescue medication (acetaminophen [paracetamol]).

5.1.6 Visit 14 (24 hours following Visit 13, post-injection telephone call)

The following procedures will be performed at Visit 14:

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

5.1.7 Visit 15 (Day 252 ± 14 days, in-clinic); Week 36

The following procedures will be performed at Visit 15:

- Perform and record physical examination.(prior to injection)
- Record vital signs. (Measure body temperature, systolic / diastolic blood pressure [BP] and pulse rate) pre- and post-injection.
- Complete the WOMAC Index 3.1. for the study knee (prior to injection)
- Complete the PGA for the study knee (prior to injection)
- Perform intra-articular injection of study drug.
- Record post-injection AEs if observed.
- Record concomitant medications.
- Review/Issue rescue medication (acetaminophen [paracetamol]).

5.1.8 Visit 16 (24 hours following Visit 15, post-injection telephone call)

The following procedures will be performed at Visit 16:

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

5.1.9 Visit 17 (Day 280 ± 14 days, in-clinic final visit); Week 40

The following procedures will be performed at Visit 17:

- Perform and record physical examination.

- Record vital signs. (Measure body temperature, systolic / diastolic blood pressure [BP] and pulse rate)
- Complete the WOMAC Index 3.1. for the study knee
- Complete the WOMAC Index 3.1 for the contralateral knee
- Complete the PGA for the study knee
- Record if subject was able to delay TKR by participation in study
- Record AEs if observed.
- Record concomitant medications.
- Draw safety labs
- Obtain x-ray of study knee
- Review/Collect rescue medication (acetaminophen [paracetamol]).

5.1.10 Early Termination Visit

The following procedures will be performed at Early Termination Visit:

- Perform and record physical examination.
- Record vital signs. (Measure body temperature, systolic / diastolic blood pressure [BP] and pulse rate)
- Complete the WOMAC Index 3.1. for the study knee
- Complete the WOMAC Index 3.1 for the contralateral knee
- Complete the PGA for the study knee
- Record if subject was able to delay TKR by participation in study
- Record AEs if observed.
- Record concomitant medications.
- Draw safety labs
- Obtain x-ray of study knee (excluding subjects who terminate in order to receive TKR)
- Review/Collect rescue medication (acetaminophen [paracetamol]).

5.1.11 Unscheduled Visits

Additional visits may be scheduled at the discretion of the Investigator, for example as part of follow up of AEs.

5.1.12 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 follow up visit, the visit is considered missed.

5.1.13 CONCOMITANT MEDICATIONS

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

1. No IA injected pain medications in the study knee during the study. HA and steroid injections in the contralateral knee are acceptable while on study except ± 14 days of Ampion injection in the study knee.
2. No analgesics containing opioids.
3. NSAIDS may not be used ± 72 hours before/after IA injection of Ampion (in-office visits). Low-dose Aspirin (81 mg) is allowed but should not be used at least 24 hours prior to an in-office visit. 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 osteoarthritis study knee during the study.
6. No significant anticoagulant therapy (e.g. Heparin or Lovenox) during the study (treatment such as Aspirin 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 be recorded.

The provided rescue medication during the 40-week extension 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 9 (Day 0), subject demographic data will be collected. These include: year of birth, age, gender and race.

Medical History

At Visit 9 (Day 0) 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 9 (Day 0). Concomitant medications (especially any changes in medication) will be documented for each subject at each scheduled visit.

Physical Examination and Vital signs

Height in feet and inches will be measured at Visit 9 (Day 0).

Body weight in pounds (lb) will be measured at Visit 9 (Day 0).

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 study knee will consist of evaluating the knee joint for effusion and tenderness on palpation.

Kellgren-Lawrence Grading Scale

Radiographic images are evaluated according to the Kellgren-Lawrence Grading Scale as noted below in Figure 2, as assessed in the Main Study

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

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 should be completed by subjects at each in-clinic visit, pre-dose. 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 study knee (study joint) due to arthritis during the last 24 hours. This will be assessed at every in-office visit.

Subjects will also be asked about their pain, stiffness, and function in the non-study knee. This will be assessed at Enrollment and Visit 17 (or early termination visit).

Subjects respond to each subscale by using a 5-point adjectival 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 each in-clinic visit (prior to injection).

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 placebo were found, safety will be assessed by recording adverse events, vital signs, results of physical examination, by recording prior and concomitant medications, and safety labs (at the Visit 17/Early Termination visit only).

6.2.1 Vital Signs

Vital signs (radial pulse rate, blood pressure, and body temperature) should be recorded at each in-clinic visit, both pre-and post-dose (as applicable).

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 will have lab tests at Visit 17 (or Early Termination) to evaluate for changes from Screening (Visit 1) of the Main Study.

The following analysis will be conducted:

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.

TABLE 6.1 SCHEDULE OF ASSESSMENTS AND PROCEDURES

	Enrollment[1]	Post-treatment phone contact	Week 12	Post-treatment phone contact	Week 24	Post-treatment phone contact	Week 36	Post-treatment phone contact	Week 40 Final Visit	Early Termination
Visit # Day #	**9[1] Day -170 to Day 0**	**10 24 hours following Visit 9**	**11 Day 84 ± 14 days**	**12 24 hours following Visit 11**	**13 Day 168 ± 14 days**	**14 24 hours following Visit 13**	**15 Day 252 ± 14 days**	**16 24 hours following Visit 15**	**17 Day 280 ± 14 days**	**18 Early Termination**
Informed Consent	X									
Inclusion/exclusion criteria	X									
Medical history/prior medications	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Physical examination	X		X		X		X		X	X
Vital Signs	X		X		X		X		X	X
WOMAC[2]	X[2]		X		X		X		X[2]	X[2]
Subject's global assessment (PGA)	X		X		X		X		X	X
X-ray	X[3]								X	X[8]
Clinical laboratory tests									X	X
Urine Analysis[4]	X[4]									
Treatment with study drug	X		X		X		X			
Rescue medication[5]	X[5]		X		X		X		X	X
Review Rescue medication[6]	X[6]	X	X	X	X	X	X	X	X	X
Adverse Events[7]	X	X	X	X	X	X	X	X	X	X

1. Subjects have 170 days to roll over from the AP-003-C main study (Visit 7) to this AP-003-C-OLE study (Visit 9). The first injection of the AP-003-C-OLE study is considered "Day 0". Visit 8 is accounted for in the AP-003-C main study in the event of Early Termination.
2. WOMAC also assessed for contralateral knee at Visit 9 and Visit 17 (or Early Termination visit, if applicable).
3. X-ray as assessed during Screening of AP-003-C main study.

4. For women of child-bearing potential, a HCG urine analysis must be completed at Visit 9 prior to enrollment in AP-003-C-OLE study to verify subject is not pregnant.
5. Rescue medication provided at Visit 9 and then as needed throughout the study. Bottles must be collected prior to dispensing a new bottle and at termination of AP-003-C-OLE study.
6. Use of rescue medication should be reviewed during each visit.
7. AEs at Visit 9 should be evaluated for ongoing AEs from the AP-003-C main study (pre-injection) and AEs occurring after injection.
8. X-ray to be obtained at Visit 18 unless subject terminates in order to get TKR. X-ray is unnecessary in this case.

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. Sites should record the specific reason for withdrawing. Subjects 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 receive a single intra-articular injection every 12 weeks into one knee of Ampion™ at a volume of 4ml.

8.1 DOSING AND ADMINISTRATION OF STUDY MEDICATION

Appropriately trained site personnel should administer the study treatment.

It is required that the same study knee assessed in the AP-003-C main study be the same study knee in the AP-003-C-OLE study. At the time of dose administration, the study knee should be treated with received investigational product. The other knee should receive standard of care.

It is recommended that the study treatment 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) to a subject who is 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, sub-dermal anesthesia, or nothing is appropriate. Intra-articular injection of lidocaine or other numbing agents are not allowed.

The recommended needle of choice for this injection is a 25-gauge needle that is 1.5 inches long. The needle may 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 (band aid) is used to cover the injection site. Injection should proceed easily. Failure to easily inject should be documented as a potential non-inter-articular injection.

The 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, etc.). 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. Temperature monitors, and instructions to download the temperature data to Ampio Pharmaceuticals, Inc., will be included with each site shipment of study drug.

The Investigator, the clinical site pharmacist, 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.

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, 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 the full 4.0 mL injection volume was administered. 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-subject 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-subject 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 their first IA injection at the Baseline visit of the AP-003-C main study through subject's Final Visit 17 at 40 weeks of AP-003-C-OLE study. 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 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. 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 Contact 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.

10.1.1 Statistical and Analytical Plan:

This is an open-label study to evaluate the safety of intra-articular Ampion™ every 12 weeks over a total course of 52 weeks (12 weeks in AP-003-C main study and an additional 40 weeks in AP-003-C-OLE study) in subjects with OA of the knee. Safety will be assessed by recording AEs at all visits, recording concomitant medications, physical exams, and vital signs at all in-clinic visits, and obtaining labs at the final study visit (Visit 17 or Early Termination Visit 18 only).

Efficacy of repeat injections will be analyzed as exploratory endpoints. Efficacy variables will be assessed at all in-clinic visits.

10.2 STUDY OBJECTIVES

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

The exploratory objectives are to analyze the efficacy of a 4-mL intra-articular (IA) injection of Ampion™ with repeat dosing every 12 weeks for 52 weeks and/or with five total injections of Ampion™. Exploratory efficacy will evaluate changes in pain, stiffness and function using the validated WOMAC 3.1 Index and PGA.

10.3 ANALYSIS POPULATIONS

10.3.1 Safety Analysis Population:

The safety analysis population is defined as all subjects who are enrolled in the AP-003-C-OLE study and receive at least one dose of study medication (Ampion™). 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 enrolled and receive at least one dose of study medication (Ampion™). 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 and had no major protocol violations as determined by the sponsor prior to analysis. 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 Statistical Analysis of Exploratory Effectiveness Endpoint

Since there are multiple injections administered over time, the stability and/or improvement of WOMAC and PGA scores between successive administrations will be investigated.

10.3.5 Primary Hypotheses for Exploratory Endpoints

The evaluation of efficacy is an exploratory endpoint and as such no formal hypothesis testing will be performed against a threshold of success. However, since there are multiple injections administered over time, the stability of pain scores will be evaluated between successive administrations to determine if the difference is zero. This will be evaluated by utilizing two sided 95% confidence intervals.

10.3.6 Definition of Study Visits

This clinical trial has a total of 9 study visits, including telephone contacts, during the 40-week study (see Table 6.2). The time-on-study for each subject observation will be defined relative to Day 0 of the initial dose of the AP-003-C main study. For the proposed summaries of the data, several "baseline" measures will be utilized.

10.3.7 Number of subjects to receive study drug

Planned enrollment is up to 161 subjects; all subjects that consent to participate in the AP-003-C-OLE study. Assuming a 15% dropout rate, a total of 136 subjects will be enrolled.

10.3.8 Disposition of subjects

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

10.3.9 Interim analysis

An interim analysis will occur when approximately 80 subjects have reached 52 weeks of time following the first injection at Visit 1 of the AP-003-C main study, regardless of what study visit they have completed in the AP-003-C-OLE study.

10.3.10 Blinding and randomization

No blinding or randomization is required for the AP-003-C-OLE study. All subjects will receive Ampion™ 4-mL at each in-clinic visit.

10.3.11 Data presentation

10.3.11.1 Demographic and Baseline Characteristics:

Demographic (e.g., age, sex, race, ethnicity) and baseline characteristics (e.g., weight, height) 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 enrollment will be presented overall and by treatment group for the ITT analysis population. Results of any abnormalities documented from the physical examination will be summarized overall and by treatment group 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 and by treatment group 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 and by treatment group for the safety and ITT analysis populations.

10.3.11.4 Safety data:

Safety data will be evaluated by changes in vital sign measurements 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 to be 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 completion of the study at Visit 17 or until early termination from the study (if applicable).

Investigators are required to document all AEs occurring during the clinical trial, commencing with the first day of treatment and including the protocol-defined post-treatment follow-up period 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.

10.3.11.5 Efficacy data:

All efficacy variables will be assessed at Visit 9 (Day 0), Visit 11 (Day 84 ± 14), Visit 13 (Day 168 ± 14), Visit 15 (Day 252 ± 14), and Visit 17 (Day 280 ± 14). Except where noted to be otherwise, all statistical tests will be two-sided and will be at the 5% level of significance.

Unless otherwise specified, continuous variables will be summarized with the number of non-missing observations, mean, standard deviation, median, minimum, and maximum displayed. Categorical data will be summarized as counts and percentages. All efficacy assessments will be summarized as the measured value and as the change from baseline by treatment at each time point. Summary statistics will include number of observations, mean, standard deviation, median, minimum and maximum. Change from baseline will also include a 95% confidence interval.

Except where otherwise specified, missing data will not be estimated or carried forward in any of the descriptive analyses. No multiple comparison adjustment will be made for the secondary efficacy analyses. Data transformation or use of rank-based tests may be used if endpoints depart substantially from a normal distribution.

Baseline (Day 0 of AP-003-C main study) is defined as the last pre-treatment assessment. Because the secondary analyses are considered supportive to the primary analysis (i.e., not required to demonstrate efficacy of the test article), there is no requirement under ICH to adjust for multiplicity

10.4 STUDY ENDPOINTS

10.4.1 Primary Endpoint

- Incidence and severity of treatment-emergent adverse events (TEAEs).

These incidents will be summarized by number and percent of subjects having an event, the number of events per subject, and frequency of events in study population.

10.4.2 Exploratory Endpoints

- Responder status based on the OMERACT-OARSI responder criteria from Enrollment/Visit 9 (Day 0) to Visits 11, 13, 15, and 17
- Evaluate 20% improvement in Pain and Function and 0.5 point absolute change in the 5-point Likert Scale from Enrollment/Visit 9 (Day 0) to Visits 11, 13, 15, and 17
- Evaluate 20% improvement in PGA and 0.5 point absolute change in the 5-point Likert Scale
- Mean change in WOMAC A pain subscore between Visit 1/Day 0 (AP-003-C main study) and Enrollment/Visit 9 (Day 0) to Visits 11, 13, 15, and 17 (AP-003-C-OLE)
- Percent change in WOMAC A pain subscore between Visit 1/Day 0 (AP-003-C main study) and Enrollment/Visit 9 (Day 0) to Visits 11, 13, 15, and 17 (AP-003-C-OLE)
- Mean change in WOMAC B stiffness subscore between Visit 1/Day 0 (AP-003-C main study) and Enrollment/Visit 9 (Day 0) to Visits 11, 13, 15, and 17 (AP-003-C-OLE)
- Percent change in WOMAC B stiffness subscore between Visit 1/Day 0 (AP-003-C main study) and Enrollment/Visit 9 (Day 0) to Visits 11, 13, 15, and 17 (AP-003-C-OLE)
- Mean change in WOMAC C physical function subscore between Visit 1/Day 0 (AP-003-C main study) and Enrollment/Visit 9 (Day 0) to Visits 11, 13, 15, and 17 (AP-003-C-OLE)
- Percent change in WOMAC C physical function subscore between Visit 1/Day 0 (AP-003-C main study) and Enrollment/Visit 9 (Day 0) to Visits 11, 13, 15, and 17 (AP-003-C-OLE)
- Mean change in PGA between Visit 1/Day 0 (AP-003-C main study) and Enrollment/Visit 9 (Day 0) to Visits 11, 13, 15, and 17 (AP-003-C-OLE)
- Percent change in PGA between Enrollment/Visit 9 (Day 0) to Visits 11, 13, 15, and 17 (AP-003-C-OLE)
- Mean Change in WOMAC A pain subscore questions 1 and 2 (pain with movement) between Visit 1/Day 0 (AP-003-C main study) and Enrollment/Visit 9 (Day 0) to Visits 11, 13, 15, and 17 (AP-003-C-OLE)

- Percent Change in WOMAC A pain subscore questions 1 and 2 (pain with movement) between Visit 1/Day 0 (AP-003-C main study) and Enrollment/Visit 9 (Day 0) to Visits 11, 13, 15, and 17 (AP-003-C-OLE)
- Mean Change in WOMAC A pain subscore questions 3−5 (resting pain) between Visit 1/Day 0 (AP-003-C main study) and Enrollment/Visit 9 (Day 0) to Visits 11, 13, 15, and 17 (AP-003-C-OLE)
- Percent Change in WOMAC A pain subscore questions 3−5 (resting pain) between Visit 1/Day 0 (AP-003-C main study) and Enrollment/Visit 9 (Day 0) to Visits 11, 13, 15, and 17 (AP-003-C-OLE)
- Change in contralateral knee pain (WOMAC A) between Visit 9 and Visit 17
- Change in contralateral knee stiffness (WOMAC B) between Visit 9 and Visit 17
- Change in contralateral knee function (WOMAC C) between Visit 9 and Visit 17
- Time to Total Knee Replacement (TKR)
- Use of rescue analgesia (amount of acetaminophen used)

Exploratory efficacy analyses include the mean change and percent change in WOMAC A, WOMAC B, WOMAC C, WOMAC A1-2, WOMAC A3-5, PGA and amount of acetaminophen used from Visit 1 to Visit 17 using an analysis of covariance model, adjusted for baseline value.

Percent responders using the OMERACT-OARSI responder criteria will be analyzed defined as the percent of subjects whom respond to treatment from Visit 1 to Visit 17. Interim visits will also be analyzed.

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. subject's global assessment ≥ 20% and absolute change in Likert score ≥0.5

All of the above endpoints will be evaluated via descriptive statistics and confidence intervals.

The WOMAC Pain Score, the WOMAC Function Score, then PGA score and the OMERACT-OARSI responder criteria, will be analyzed via a repeated measures analysis of variance to determine if there is a significant time effect for these endpoints. Also, to aid in the interpretation of these results, a stability analysis will be performed on these same endpoints. That is, mean pairwise differences between administration time points will be calculated along with their 95% confidence intervals. If stability is achieved at some time point, then the following mean differences should be not be different from zero, in that the confidence interval should include zero.

Adverse events will be tabulated for both number of subjects and number of events by subject and overall study population, summarized by any event, body system, and preferred term. Summaries by serious, severity, and relationship will also be done.

10.5 MISSING AND SPURIOUS DATA

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

For the exploratory effectiveness endpoint analyses (WOMAC and PGA), missing scores will be imputed in when the worst observation carried forward to aid in the assessment of the robustness of the results.

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 Harmonization (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 that 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 one 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, 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, x-ray, 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, x-ray, 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 eCRFs, 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 document.

12 REFERENCES

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13 APPENDICES

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