

THE GID GROUP

CLINICAL RESEARCH PROTOCOL

**USE OF AUTOLOGOUS ADIPOSE-DERIVED STROMAL
VASCULAR FRACTION TO TREAT OSTEOARTHRITIS OF THE
KNEE: A CONTROLLED, RANDOMIZED, DOUBLE-BLINDED
TRIAL**

Protocol Number:	GIDOA-01
Date and Version Number:	October 1, 2015 Ver. 3.0
Investigational Device:	GID SVF-2
Study Phase:	Pivotal
Sponsor-Investigator:	The GID Group 901 Front St. Suite 240 Louisville, CO 80026
Funding Organization:	NA
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Approval:

PI or Sponsor Signature (Name and Title)

Date

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing The GID Group with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: GIDOA-01

Protocol Title: Use of Autologous Adipose-Derived Stromal Vascular Fraction to Treat Osteoarthritis of the Knee: A Controlled, Randomized, Double-Blinded Trial

Protocol Date: October 1, 2015

Investigator Signature

Date

Print Name and Title

Site #

Site Name

Address

Phone Number

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LIST OF ABBREVIATIONS

ADSC	adipose-derived stromal cells
AE	adverse event
ASA	American Society of Anesthesiologists
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HR	heart rate
ICD	informed consent document
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IRB	Institutional Review Board
K-L Scale	Kellgren-Lawrence Osteoarthritis Scale <ul style="list-style-type: none">• Grade 0, None – No radiographic features of OA are present• Grade 1, Doubtful – Doubtful narrowing of joint space and possible osteophytic lipping• Grade 2, Minimal – Definite osteophytes and possible narrowing of joint space on anteroposterior weight-bearing radiograph• Grade 3, Moderate – Moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends• Grade 4, Severe – Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends
LR	lactated Ringer's
OA	osteoarthritis
PI	Principal Investigator
RR	respiratory rate
SAE	serious adverse event
SVF	stromal vascular fraction
UADE	unanticipated adverse device effect
UAE	unanticipated adverse event
VAS	visual analog scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

PROTOCOL SYNOPSIS

TITLE	Use of Autologous Adipose-Derived Stromal Vascular Fraction to Treat Osteoarthritis of the Knee: A Controlled, Randomized, Double-Blinded Trial
SPONSOR	The GID Group
FUNDING ORGANIZATION	NA
NUMBER OF SITES	Up to 3 sites
RATIONALE	<p>This study will examine the safety and efficacy of autologous adipose-derived stromal vascular fraction (SVF) cells processed with the GID SVF-2 device for pain, function and stiffness in the knees of osteoarthritic subjects.</p> <p>Osteoarthritis is the main form of arthritis and affects over 20 million people in the United States. In the knee it can cause severe pain, reduced functionality and increased stiffness thus, a treatment that would reduce pain, increase function and reduce stiffness would be of benefit to many people.</p>
STUDY DESIGN	This is a multi-center, prospective, randomized, blinded, interventional safety and efficacy study.
PRIMARY OBJECTIVE	To evaluate the safety of a single injection of autologous adipose-derived SVF for treatment of osteoarthritis of the knee.
SECONDARY OBJECTIVE	To evaluate the initial efficacy of a single injection of autologous adipose-derived SVF for reduction of pain and stiffness and increased functionality in patients with osteoarthritis of the knee.
NUMBER OF SUBJECTS	39
SELECTION CRITERIA	<p><u>Inclusion Criteria:</u></p> <ol style="list-style-type: none"> Grade II or Grade III osteoarthritis using Kellgren-Lawrence grading scale (K-L Grade) as diagnosed using weight bearing X-ray, physician review, and/or pre-op MRI Study Subjects must have failed a minimum of at least two conservative therapies, spanning a period of at least 3 months, including (i) oral pain medications, (ii) physical therapy, (iii) corticosteroid injection of the knee, (iv) viscosupplementation injection of the knee Study Subjects must be willing to voluntarily give written Informed Consent to participate in the study and sign the Health Insurance Portability and Accountability Act (HIPAA) authorization before any study procedures are performed Males and females 40-75 years old Subjects will be in good health (ASA Class I-II) with a BMI < 35

	<ol style="list-style-type: none"> 6. Subjects must have continued pain in the knee despite conservative therapies for at least 3 months 7. Subjects with unilateral disease must present with a knee pain score ≥ 6 and ≤ 16 using the short-form WOMAC pain (A1 subscale, 20 total points) 8. Subjects with bilateral disease will only be treated in one knee. The treated knee must have K-L grade II or III with a pain score ≥ 6 and ≤ 16 using the short-form WOMAC pain (A1 subscale, 20 total points) and the contralateral knee has a K-L grade of I or II with a pain score < 6 using the short-form WOMAC pain (A1 subscale, 20 total points) 9. Subjects must speak, read and understand English 10. Subjects must be reasonably able to return for multiple follow-up visits <p><u>Exclusion Criteria:</u></p> <ol style="list-style-type: none"> 1. Subjects whose knee pain is caused by, (i) diffuse edema, (ii) displaced meniscus tear, (iii) lesion greater than 1 cm in any direction, or (iv) osteo chondritis desicans 2. Subjects who have had surgery of either knee within 6 months prior to the screening visit 3. Subjects who have had a major injury to the targeted/treatment knee within 12 months prior to enrolling in the study 4. Subjects who have had an injection in either knee in the prior 3 months, including corticosteroids, viscosupplementation or platelet rich plasma (PRP) 5. Subjects who have gout, rheumatoid arthritis, lupus arthropathy, psoriatic arthritis, avascular necrosis, severe bone deformity, infection of the knee joint, fibromyalgia, pes anserine bursitis, or neurogenic or vascular claudication. 6. Subjects who have symptomatic OA of the hips, spine, or ankle that would interfere with the evaluation of the treated knee 7. Subjects that are unwilling to stop taking prescription or over the counter pain medication 7 days prior to any visit 8. Subjects that are allergic to lidocaine, epinephrine or valium 9. Subjects with a history of bleeding disorders, anticoagulation therapy that cannot be stopped as follows prior to injection; Thrombolytics and anti-platelet medication including but not limited to Coumadin (warfarin) for 3 days, Plavix (colpidogrel) for 3 days, ASA/NSAIDs/fish oil supplements for 7 days, Xeralta® (rivaroxaban) for 24 hours
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	<p>10. Subjects with systemic immunosuppressant use within six (6) weeks from screening and subjects with HIV/viral hepatitis</p> <p>11. Subjects with chondrocalcinosis, Paget’s disease and Villonodular synovitis</p> <p>12. Subjects that use any form of tobacco</p> <p>13. Women that are pregnant or planning to become pregnant during the study</p> <p>14. Subjects on long term use of oral steroids</p> <p>15. History of any chemotherapy or radiation therapy on the targeted/treatment leg or adipose harvest site</p> <p>16. Subjects currently on worker’s compensation</p>
<p>INVESTIGATIONAL DEVICE / INTENDED USE</p>	<p>GID SVF-2</p> <p>The GID SVF-2 device is indicated for use for harvesting, filtering, separating, and concentrating autologous stromal vascular fraction cells from adipose tissue for reintroduction to the same patient during a single surgical procedure for treatment of pain associated with joint osteoarthritis. The GID SVF-2 device is to be used only with the GID SVF Procedure Pack.</p>
<p>CONTROL GROUP</p>	<p>This study is a 3-arm study with a placebo control group. The study arms are: 1) low-dose group (15 million SVF cells in 4 ml of lactated Ringer’s (LR)), 2) high-dose group (30 million SVF cells in 4 ml of LR), and placebo control group (0 SVF cells in 4 ml of LR).</p>
<p>DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY</p>	<p>Subjects may have up to 4 weeks between screening and treatment. After treatment follow-up visits will be at 2 days, 6 weeks; 3 and 6 months; with safety follow-up phone calls or visits at 1 and 2 years.</p> <p>Subject Screening: up to 4 weeks</p> <p>Subject Treatment: 1 day</p> <p>Subject Follow-up: 6 months</p> <p>Subject Safety Follow-up: 2 years</p> <p>The total duration of the study is expected to be 1 year (6 months to complete recruiting and 6 months to complete follow-up) with safety follow-up completing within 3 years.</p>
<p>CONCOMITANT MEDICATIONS</p>	<p>The following medications should be stopped or are not allowed during the study as follows:</p> <p>ANY Pain Medication 7 DAYS PRIOR to any Visit.</p> <p>Prior to Surgery the subject may not take any medications and over-the-counter drugs as follows:</p> <p>a. 14 days Prior to Surgery</p> <ul style="list-style-type: none"> • Oral steroids that are short course (less than 14 days total)

	<p>b. 7 days Prior to Surgery</p> <ul style="list-style-type: none"> • Pain medications (all); • ASA/NSAIDs/fish oil supplements <p>c. 3 days Prior to Surgery -</p> <ul style="list-style-type: none"> • Thrombolytics and anti-platelet medication including but not limited to Coumadin (warfarin), Plavix (colpidogrel) <p>d. 24 hours Prior to Surgery –</p> <ul style="list-style-type: none"> • Xeralta® (rivaroxaban) <p>After Surgery the subject may not take any medications and over-the-counter drugs as follows:</p> <p>a. For 24 hours After Surgery –</p> <ul style="list-style-type: none"> • Xeralta® (rivaroxaban) <p>b. For 3 days After Surgery -</p> <ul style="list-style-type: none"> • Thrombolytics and anti-platelet medication including but not limited to Coumadin (warfarin), Plavix (colpidogrel), • ASA/NSAIDs/fish oil supplements <p>c. Oral steroids for duration of study</p> <p>All concomitant medications will be recorded on the Concomitant case report form at each subject follow-up visit.</p>
SAFETY EVALUATIONS	Incidence and severity of adverse events and comparison of MRI images from baseline to 6 months for any unusual findings.
EFFICACY EVALUATIONS & PRIMARY ENDPOINT	<p>Pain, function and stiffness will be compared at baseline and 6 months post-operatively using the validated short-form of the WOMAC instrument and a Visual Analog Scale (VAS) for pain.</p> <p>Efficacy will be achieved if either SVF dose is shown to be superior to the placebo group at the 6-month time point. The measures of interest are from baseline to 6 months of the changes in the WOMAC and VAS pain scales and comparison to the placebo control group.</p>
PLANNED INTERIM ANALYSES	After the first 15 subjects have completed the 6 week follow-up, an interim analysis for safety will be conducted. If there are two (2) or fewer adverse events less than grade 4 on the Common Terminology Criteria for Adverse Events (CTCAE) scale, then the high dose will be administered. Serious adverse events will be monitored on an ongoing basis throughout the study and safety follow-up period.
STATISTICS	The primary efficacy will be evaluated using Dunnett’s multiple comparison with a control test.
RATIONAL FOR NUMBER OF SUBJECTS	The samples size determination is based on the primary efficacy endpoint using the WOMAC score (scaled to 100 points full scale) and evaluated using Dunnett’s multiple

	<p>comparison with a control one-sided (i.e., superiority) test. Assuming a standard deviation of 14 points and a difference to detect (i.e., minimal clinically significant difference) of at least 17 (representing about a 33% decrease from baseline) points with an $\alpha = 0.05$ significance level and a power of 80% a conservative sample size of 11 subjects per group is needed. This sample size estimate is based on a Bonferroni correction and as such is conservative (i.e., larger than necessary). Thus, the goal will be to have no fewer than 11 subjects per treatment group. To account for possible exclusions/lost to follow-up of data an additional 2 subjects per treatment group (20%) will be added for a sample size of 13 subjects per group for a total enrolled sample size of 39 subjects.</p>
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1 PURPOSE OF THE INVESTIGATION

1.1 Overview of Investigation and Clinical Plan

Osteoarthritis (OA) is known as degenerative arthritis or degenerative joint disease or osteoarthrosis, and represents a group of mechanical abnormalities involving degradation of joints, including the articular cartilage and subchondral bone. Symptoms typically may include joint pain, tenderness, stiffness, locking, and sometimes effusion. Clinical treatment generally involves a life-long combination of exercise, lifestyle modifications, and/or analgesics. If pain becomes debilitating, joint replacement surgery may be an option to improve the quality of life.

A new and novel treatment strategy has had preliminary success in preclinical studies as well as in pilot clinical studies that have utilized the autologous stromal vascular fraction (SVF) cells derived from adipose tissues. The SVF is a concentration of nucleated cells normally present in the adipose tissue. This treatment strategy uses the autologous SVF cells derived from harvested adipose tissue within a single clinical procedure (bedside). The adipose tissue is harvested under sterile conditions, then washed, then dissociated using enzymatic digestion, then the SVF cells are concentrated and returned to the patient using a syringe injection to the joint space.

This IDE application addresses the GID SVF-2 medical device and GID SVF Procedure Pack produced by The GID Group, Inc. for collection and processing of adipose tissue including collect, wash, dissociate, separate, and concentrate SVF cells from human lipoaspirate. The GID Group, Inc. and its contract manufacturer are both FDA-registered and audited, MDD certified, and ISO13485:2003 certified companies. Both maintain a Quality Management System (QMS) compliant with the Quality System Regulation (QSR) to provide the framework of controls for the facility and processes employed in the manufacture, assembly, labeling and distribution of medical devices.

This clinical trial with this IDE proposal is a multi-center, randomized, double-blinded, controlled clinical study to investigate the safety and efficacy in the use of adult autologous adipose SVF for the treatment of pain associated with joint

OA. The hypothesis of this trial is that the proposed clinical outcome measures of reduced pain resulting from the treatment of OA of the knee joint with autologous adipose SVF tissue will be superior to a placebo control treatment.

1.2 Name of Investigational Device

GID SVF-2 and GID SVF Procedure Pack

1.3 Intended use of the investigational device

The GID SVF-2 device is indicated for use for harvesting, filtering, separating, and concentrating autologous stromal vascular fraction cells from adipose tissue for reintroduction to the same patient during a single surgical procedure for treatment of pain associated with joint osteoarthritis. The GID SVF-2 device is to be used only with the GID SVF Procedure Pack.

All materials supplied for the proposed study are for investigational use only and are to be used solely within the context of the approved protocol.

1.4 Objectives of the clinical investigation

1.4.1 Primary objective

Evaluate the safety of the GID SVF-2 for the treatment of osteoarthritis in the knee in humans.

1.4.2 Secondary objectives

Evaluate the efficacy of the GID SVF-2 for the treatment of osteoarthritis of pain, stiffness and functionality associated with osteoarthritis of the knee in humans.

1.5 Anticipated Duration of the clinical investigation

It is anticipated that the trial duration will not exceed 1 year; 6 months for recruitment and 6 months follow-up with an additional 2 years for safety follow-up.

2 CLINICAL PROTOCOL

2.1 Protocol number and title

GIDOA-01: Use of Autologous Adipose-Derived Stromal Vascular Fraction to Treat Osteoarthritis of the Knee: A Controlled, Randomized, Double-Blinded Trial

2.2 Protocol version, number and date

Version 3.0, GIDOA-01, October 1, 2015

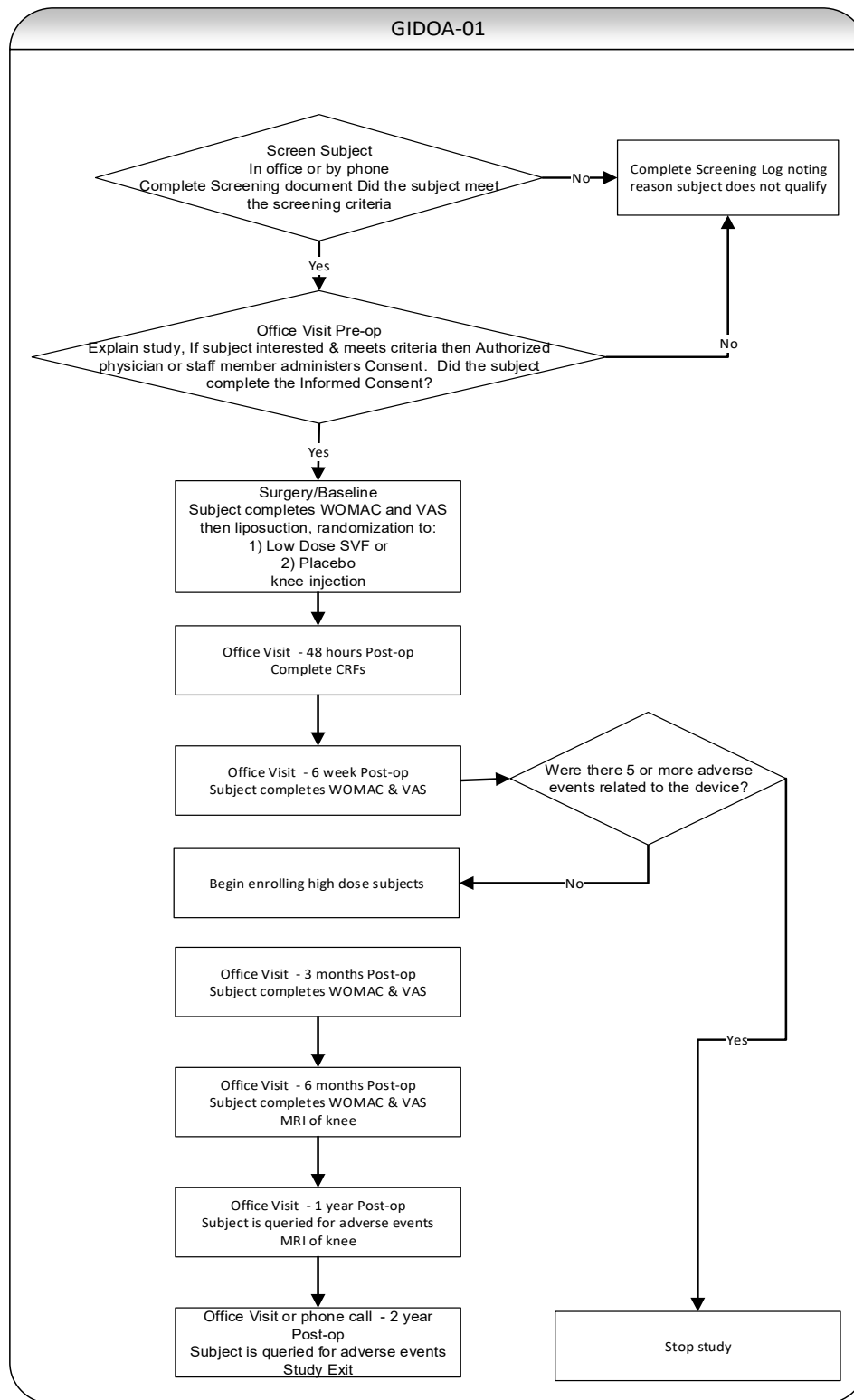
2.3 Study design

2.3.1 General study design

This is a multi-center, prospective, randomized, blinded, interventional safety and efficacy study. The study is designed as a dose escalation, parallel-groups design (uncorrelated, unpaired, independent groups) with

placebo control. There are three groups: treatment group high dose (H) receives injection of 4 cc of LR with 30 million SVF cells; treatment group low dose (L) receives injection of 4 cc of LR with 15 million SVF cells; placebo control group (C) receives injection of 4 cc of LR with zero SVF cells (Figure 2).

An SVF dose escalation design will be included in the study. The first fifteen (15) subjects will be randomized to low dose or placebo as follows: nine (9) subjects will receive the low SVF dose (15×10^6 cells) and six (6) subjects will receive the placebo (no SVF cells). When all fifteen (15) subjects have reached the 6 week follow up the cohort of 15 will be evaluated for adverse events and any safety issues. If there are two or less adverse events of less than grade 4 on the Common Terminology Criteria for Adverse Events (CTCAE) scale in the low SVF dose group, then the remaining twenty-four (24) subjects will be randomized to receive the following doses: four (4) subjects will receive the low SVF dose (15×10^6 cells), thirteen (13) subjects will receive the high SVF dose (30×10^6 cells) and seven (7) subjects will receive the placebo dose.

2.3.2 Study design schematic

Figure 1 Study Flow Schematic

2.4 Subject selection

2.4.1 General characteristics of the proposed subject populations

Subjects will consist of males and females between the ages of 40 and 75 with Kellgren-Lawrence OA grading scale (K-L Grade) II or III and a WOMAC pain score $\geq 6 \leq 16$ on a 20 point scale in one knee and a WOMAC pain score ≤ 6 for the contralateral knee if the subject has bilateral disease.

2.4.2 Anticipated number of research subjects

Enrollment was determined to be 39 based on a minimally clinically significant difference of 17 points on the WOMAC pain score with an $\alpha = 0.05$ significance level and a power of 80% (11 subjects/group) plus an additional 2 subjects per group (20%) for lost to follow up.

2.4.3 Inclusion criteria

1. Grade II or Grade III osteoarthritis using Kellgren-Lawrence grading scale (K-L Grade) as diagnosed using weight bearing X-ray, physician review, and/or pre-op MRI.
2. Study Subjects must have failed a minimum of at least two conservative therapies, spanning a period of at least 3 months, including (i) oral pain medications, (ii) physical therapy, (iii) corticosteroid injection of the knee, (iv) viscosupplementation injection of the knee.
3. Study Subjects must be willing to voluntarily give written Informed Consent to participate in the study and sign the Health Insurance Portability and Accountability Act (HIPAA) authorization before any study procedures are performed.
4. Males and females 40-75 years old.
5. Subjects will be in good health (ASA Class I-II) with a BMI < 35 .
6. Subjects must have continued pain in the knee despite conservative therapies for at least 63 months.
7. Subjects with unilateral disease must present with a knee pain score ≥ 6 and ≤ 16 using the short-form WOMAC pain (A1 subscale, 20 total points).
8. Subjects with bilateral disease will only be treated in one knee. The treated knee must have K-L grade II or III with a pain score ≥ 6 and ≤ 16 using the short-form WOMAC pain (A1 subscale, 20 total points) and the contralateral knee has a K-L grade of I or II with a pain score < 6 using the short-form WOMAC pain (A1 subscale, 20 total points).
9. Subjects must speak, read and understand English.
10. Subjects must be reasonably able to return for multiple follow-up visits.

2.4.4 Exclusion criteria

1. Subjects whose knee pain is caused by, (i) diffuse edema, (ii) displaced meniscus tear, (iii) lesion greater than 1 cm in any direction, or (iv) osteo chondritis desicans.
2. Subjects who have had surgery of either knee within 6 months prior to the screening visit.
3. Subjects who have had a major injury to the targeted knee within 12 months prior to enrolling in the study.
4. Subjects who have had an injection in either knee in the prior 3 months, including corticosteroids, viscosupplementation or platelet rich plasma (PRP).
5. Subjects who have gout, rheumatoid arthritis, lupus arthropathy, psoriatic arthritis, avascular necrosis, severe bone deformity, infection of the knee joint, fibromyalgia, pes anserine bursitis, or neurogenic or vascular claudication.
6. Subjects who have symptomatic OA of the hips, spine, or ankle that would interfere with the evaluation of the treated knee.
7. Subjects that are unwilling to stop taking prescription or over the counter pain medication 7 days prior to any visit
8. Subjects that are allergic to lidocaine, epinephrine or valium
9. Subjects with a history of bleeding disorders, anticoagulation therapy that cannot be stopped as follows prior to injection Thrombolytics and anti-platelet medication including but not limited to Coumadin (warfarin) for 3 days, Plavix (colpidogrel) for 3 days, ASA/NSAIDs/fish oil supplements for 7 days, Xeralta® (rivaroxaban) for 24 hours.
10. Subjects with systemic immunosuppressant use within six (6) weeks from screening and subjects with HIV/viral hepatitis.
11. Subjects with chondrocalcinosis, Paget's disease and Villonodular synovitis
12. Subjects that use any form of tobacco
13. Women that are pregnant or planning to become pregnant during the study.
14. Subjects on long term use of oral steroids
15. History of any chemotherapy or radiation therapy of the targeted/treatment leg or adipose harvest site.
16. Subjects currently on worker's compensation

2.5 Study procedures

2.5.1 Screening procedures

Initial screening may be done over the phone or at the medical office. Subjects will be asked questions from a screening form and if they meet the criteria on the form will be asked if they are interested in coming back for an office screening visit. A copy of the Informed Consent Document

will be mailed to the subject. After the subject has signed the Informed Consent, the subject will be evaluated for Grade II or Grade III osteoarthritis (K-L scale) as diagnosed using X-ray, physician review, and/or pre-op MRI. If potential participant meets the grading criteria, then they will be evaluated for the remaining inclusion/exclusion criteria.

2.5.2 Concomitant Medications

The following medications should be stopped or are not allowed during the study as follows:

ANY Pain Medication 7 DAYS PRIOR to any Visit.

Prior to Surgery the subject may not take any medications and over-the-counter drugs as follows:

- a. 14 days Prior to Surgery
 - Oral steroids that are short course (less than 14 days total)
- b. 7 days Prior to Surgery
 - Pain medications (all);
 - ASA/NSAIDs/fish oil supplements
- c. 3 days Prior to Surgery
 - Thrombolytics and anti-platelet medication including but not limited to Coumadin (warfarin), Plavix (colpidogrel),
- d. 24 hours Prior to Surgery
 - Xeralta® (rivaroxaban)

After Surgery the subject may not take any medications and over-the-counter drugs as follows:

- a. For 24 hours After Surgery
 - Xeralta® (rivaroxaban)
- b. For 3 days After Surgery -
 - Thrombolytics and anti-platelet medication including but not limited to Coumadin (warfarin), Plavix (colpidogrel),
 - ASA/NSAIDs/fish oil supplements
- c. Oral steroids for duration of study

All concomitant medications will be recorded on the Concomitant case report form at each subject follow-up visit.

2.5.3 Study treatment

The subject's adipose tissue will be acquired through liposuction of the abdomen or thigh and will be suctioned directly into the GID SVF-2 device. The harvested adipose tissue will be enzymatically digested and centrifuged in the same GID SVF-2 device to produce SVF cells. The subject will then be treated with an injection in the knee of 4 ml of LR containing one of the following:

- a) Low Dose - 15×10^6 (range $12.5 \times 10^6 - 17.2 \times 10^6$) nucleated SVF cells;
- b) High Dose - 30×10^6 (range $27.5 \times 10^6 - 32.5 \times 10^6$) nucleated SVF cells; or
- c) Placebo - 0 SVF cells.

Treatment will be randomized and both the physician and subject will be blinded to the dosage.

2.5.4 Study treatment procedures

1. Liposuction

The procedure will be performed at the clinical site according to standard clinical practice for all participants.

2. Processing of Collected Fat

The fat will be processed by the processing technician, who will not be involved in safety or efficacy evaluation. Processing of the fat will be done immediately after harvest in the operating room on a sterile table that is not visible to any study personnel. The processing technician will use the GID SVF Procedure Pack for fat processing. All tissue contacting equipment (GID SVF-2, syringes, tubing) will be sterile single-use laboratory disposables. All procedures must be followed as outlined in the IFU. Figure 2 shows an overview of the adipose lipoaspirate processing.

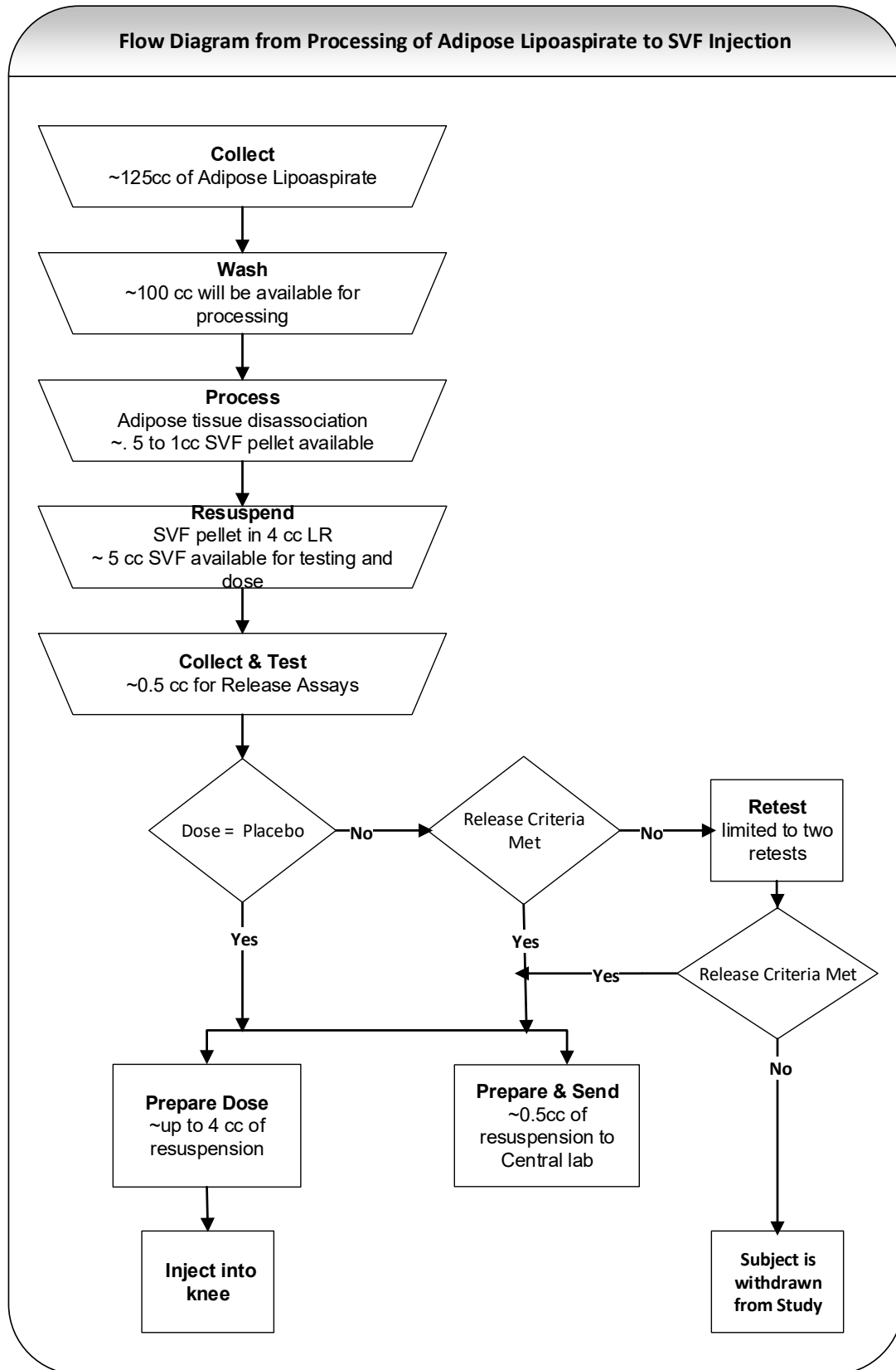


Figure 2 Overview of Adipose Lipoaspirate Processing

3. Dose Escalation, Dosing and Release Criteria

The first group of 15 subjects will be randomized to receive one of the following SVF doses:

- Low SVF dose, 15×10^6 (range $12.5 \times 10^6 - 17.5 \times 10^6$) nucleated SVF cells, suspended in 4 ml of lactated Ringer's (9 subjects) or
- Placebo control, 0 SVF cells, in 4 ml of lactated Ringer's (6 subjects)

If there are two or less adverse events of less than grade 4 on the Common Terminology Criteria for Adverse Events (CTCAE) scale, then the remaining twenty-four (24) subjects will be randomized to receive the following doses:

- Low SVF dose, 15×10^6 (range $12.5 \times 10^6 - 17.5 \times 10^6$) nucleated SVF cells, suspended in 4 ml of lactated Ringer's (4 subjects) or
- High SVF dose, 30×10^6 (range $27.5 \times 10^6 - 32.5 \times 10^6$) nucleated SVF cells, suspended in 4 ml of lactated Ringer's (13 subjects) or
- Placebo control group, 0 SVF cells, in 4 ml of lactated Ringer's (7 subjects)

Release Criterion for each injection of the SVF cells will be:

- a minimum of 70% viability (Chemometec NC-200) cells and
- total nucleated cell count in dose range (Chemometec NC-200) and
- endotoxin assessment using rapid methodology with endotoxin level ≤ 200 EU per dose and
- no gram negative detected.

The data for the cell yield, viability, endotoxin and gram ID assessments are recorded on the Cell Count Assay case report form.

Release Criteria Not Met:

- If the dose is equal to placebo, then continue with the study checking the 'Release' box on the Cell Count Assay CRF.
- If the release criteria are not met, then all criteria will be retested with only one retest allowed per release criteria.
- If the retest does not meet the release criteria, then the patient is withdrawn from the study (see Section 3.3).

Release Criteria Are Met:

- The box for ‘Release’ is checked and the processing technician signs the Cell Count Assay form.

The form will not be added to the subject’s binder until after the study has been completed and all unblinding is complete.

4. Injection of Cells

The anteromedial or superolateral portal of the treatment knee will be prepared for injection. These locations were chosen due to ease of access into the intra-articular space and to avoid injecting into the fat pad of the knee. No sedation or pain medication will be administered to the patient. An ethyl chloride topical anesthetic will be sprayed on the injection site until the skin color changes to white. Lidocaine local anesthetic will be injected using a 25 gauge needle to numb the skin and subcutaneous tissues. Verification of the needle in the intraarticular space of the knee will be done by visual evidence of synovial fluid upon aspiration or ultra sound guidance. The knee will be aspirated up to a maximum of 5 ml using an 18 gauge/1.5 inch needle. Then all of the 4 cc SVF cells suspension will be injected into the intra-articular space through the same 18 gauge/1.5 inch needle. The needle will then be removed and direct pressure over the injection site will placed for approximately ten (10) seconds. Hemostasis after injection will be confirmed, the injection site will then be cleaned with an alcohol wipe and covered with a sterile bandage. This can be removed the next morning. The patient will be given crutches and asked to be non-weight bearing on the injected knee for two (2) days. The patient will be encouraged and allowed to bend and flex the knee as long as non-weight bearing conditions are maintained. Patients will be given written instructions concerning after-injection and liposuction care and encouraged to call the administering physician at any time with questions and concerns. The patient will be asked to wait in the waiting room for 45 minutes before leaving.

2.5.5 Allocation to treatment

Subjects will be enrolled consecutively at each site. Due to the objectives of the study, the identity of test and control treatments will not be known to investigators, research staff, or subjects. The following study procedures will be in place to ensure double-blind administration of study treatments.

- Access to the randomization code will be strictly controlled and only the processing technician, who will not be involved in safety or efficacy evaluation, will know to which group the subject is randomized on the day of the surgery.
- The processing technician will process the SVF or placebo syringe out of sight of any personnel involved in the study. The technician will

mask the syringe (tape) before it is seen by any study personnel so that no one will be able to identify the treatment by sight.

2.5.6 Unblinding

The processing technician will have sole control of the Identification of Treatment by Subject log. If the need arises to unblind the treatment for a patient (i.e. adverse event) the processing technician can consult the log for treatment identification.

2.5.7 Treatment adherence

Each subject will be given an information sheet containing instructions for pre and post-operative care of their knee and liposuction site. At all of the following study visits each subject will be asked to fill out questionnaires and questioned about their knee.

2.5.8 Withdrawal of subjects due to non-compliance

Subjects may be terminated from the study at the discretion of the PI only for reasons related to the study examinations that would jeopardize the subject's health and/or welfare if they were to continue in the study. Subjects may voluntarily withdraw from the study at any time without prejudice.

Subjects who are withdrawn will not be replaced if they have received study treatment and if it is determined that there is not sufficient data for analysis the subject's data will be removed from analysis.

2.5.9 Procedures to assess efficacy

Efficacy will be determined by the change in score on the WOMAC questionnaire completed by the patient between baseline and 6 months post-op. Measurements consist of 3 sub scores; 1) pain with 5 questions and 20 total points; (2) stiffness, with 2 questions and 8 total points and (3) functionality with 7 questions and 28 total points, for a total score of 56 points, the total score will be normalized to 100 points. A decreasing score is indicative of a positive change, i.e. less pain, less stiffness and more functionality.

Additionally, at baseline, 6 weeks, 3 months and 6 months, each subject will be asked to rate their pain using a visual analog scale (VAS), a horizontal 100 mm line with anchors of 'no pain' and 'worst imaginable pain'. The patient will be asked to mark a point on the line to indicate their pain intensity when climbing or descending stairs.

2.5.10 Procedures to assess safety

Adverse events will be continuously monitored by the PIs, the independent Safety Monitor and sponsor to evaluate safety of the device and treatment up to 2 years.

MRI's will be taken pre-treatment, 6 months and 1 year according to the following sequence:

- Sequence: proton density fat saturation (PD fat sat)
- Sagittal plane only
- Magnet: 3.0T or 1.5T with knee coil (8-16 channel)

2.5.11 Schedule of study visits

Initial screening may be done over the phone or at the office. All subsequent visits will be at the site offices with the 2 year safety evaluation to be completed at the office or over the phone (Appendix A).

Prior to surgery the subjects will come into the office for an evaluation visit where they will be enrolled in the study and the inclusion/exclusion criteria will be conducted. If they qualify for the study the subject will have an MRI of their treatment knee. Subjects will return to the office 2 days post-surgery to have the surgery and injection site inspected. At the remaining 6 week, 3 month and 6 month visits the surgery and injection site will be evaluated and the subject will complete the VAS and WOMAC questionnaires. MRI's of the knee will be taken at the 6 month and 1 year visits for evaluation of any adverse changes to the joint space. At the 1 year safety follow-up visit the subject will return to the office to be evaluated for any safety concerns. Safety assessments will be completed using MRI, study questionnaires, and physical examination. It is anticipated that these visits should range from 15 minutes to 1 hour depending on the type of questions and measurements needed. The subject will be contacted 2 years after surgery for an additional safety update.

2.5.12 Subject Compensation

There will be no cost to the subjects other than the initial screening visits, which will be billed to the subject's insurance. Subjects will be given a stipend of \$350.00 to participate in the study to defray the cost to complete the 4 post-operative clinical office visits (Table 1) Subjects will receive compensation only at the time of these visits. Subjects will not be compensated for missed visits or visits outside the required 4 visits.

Table 1 Schedule of Subject Compensation

Time after Treatment	Compensation
2 days (15 minutes)	\$ 50
6 weeks (15 minutes)	\$ 50
3 months (15 minutes)	\$ 50
6 months (1 hour)	\$200
Total	\$350

2.6 Study outcome evaluations

2.6.1 Study endpoints

Safety: Safety endpoints are adverse events at any time point and MRI of the knee at 6 months and 1 year for any findings indicating that the device is not safe as used.

Efficacy: This will be achieved if either dose is shown to be superior (i.e., less pain, better function and less stiffness) to the placebo group at the 6-month time. The measure of interest is the change in the WOMAC score and VAS pain scale from baseline. The hypotheses of interest are:

$H_0: \mu_L = \mu_C \text{ and } \mu_H = \mu_C$

$H_a: \mu_L < \mu_C \text{ and/or } \mu_H < \mu_C$

2.6.2 Sample size determination

The sample size determination is based on the primary efficacy endpoint using the WOMAC score (100 points full scale) and evaluated using Dunnett's multiple comparison with a control one-sided (i.e., superiority) test. Assuming a standard deviation of 14 points and a difference to detect (i.e., minimal clinically significant difference) of at least 17 (representing about a 33% decrease from baseline) points with $\alpha = 0.05$ significance level and a power of 80% a conservative sample size of 11 subjects per group is needed. This sample size estimate is based on a Bonferroni correction and as such is conservative (i.e., larger than necessary). Thus, the goal will be to have no fewer than 11 subjects per treatment group. To account for possible exclusions/lost to follow-up of data an additional 2 subjects per treatment group (20%) will be added for a sample size of 13 subjects per group for a total enrolled sample size of 39 subjects.

2.6.3 Outcome data and data analysis

Data analysis will be performed by a trained statistician using appropriate statistical methods and software (e.g. JMP or SAS). Descriptive statistics will be presented as means, standard deviations, medians and ranges for the continuous variables and as counts and percents for categorical variables. An alpha level of 5% will be used for all analyses, unless otherwise stated. Demographics will be tabulated overall and by relevant populations. Confidence intervals will be provided where appropriate.

The primary efficacy will be evaluated using Dunnett's multiple comparison with a control test (one-sided for superiority).

The safety analysis will be descriptive and narrative in nature, with SAE's and AE's tabulated by body system, preferred term, severity and relation to procedure.

MRIs will be evaluated for any anomalies or safety issues as observed by the PI.

3 RISK ANALYSIS

3.1 Anticipated risks

The Study adds no expected risks or the need for additional safety precautions for the subject beyond what they would have for small volume liposuction surgery and a knee injection. These are detailed in the Informed Consent materials.

3.2 Adverse events and reporting

3.2.1 Adverse event definitions

Adverse Event (AE): Any untoward medical occurrence in a clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study treatment or diagnostic product(s).

Unanticipated adverse event (UAE): Any adverse effect, the frequency, specificity or severity of which is not consistent with the risk information described in the clinical study protocol(s).

Serious adverse event (SAE): An adverse event is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- death
- a life-threatening AE
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect.

Unanticipated adverse device effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

3.2.2 Eliciting adverse event information

Clinical study subjects will be routinely questioned about adverse effects at all study visits.

3.2.3 Recording and assessment of adverse events

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of treatment group, if applicable, or suspected causal relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s) will be recorded in the subjects' case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a *serious adverse event*) and; 2) an assessment of the casual relationship between the adverse event and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Adverse events or abnormal test findings felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the sponsor and investigator.

3.2.4 Abnormal test findings

An abnormal test finding (i.e. sterility of SVF) will be classified as an *adverse event* if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug or other therapy (Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse effect.)
- The test finding leads to a change in study dosing or exposure or discontinuation of subject participation in the clinical study
- The test finding is considered an adverse event by the sponsor and investigator

If a culture results in a positive sterility test it will be considered an abnormal test finding and reported to the FDA within 30 days. This report will include results of any investigation into the cause and any corrective action taken. The subject will be monitored for infection or other signs that may be attributed to the sterility failure.

If any serious or unexpected adverse events related to abnormal test findings occur due to the device, the FDA, IRB and other investigators will be notified within 10 days of first learning of the event.

3.2.5 Causality and severity assessment

The sponsor, safety monitor and investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the

investigational device or other study treatments; and 3) if the adverse event meets the criteria for a *serious adverse event*. Adverse events will be scaled according to Common Terminology Criteria for Adverse Events (CTCAE, ver. 4.03: June 14, 2010).

If the sponsor, safety monitor and/or investigator's final determination of causality is "unknown and of questionable relationship to the investigational device or other study treatments," the adverse event will be classified as *associated with the use of the investigational device or other study treatments* for reporting purposes. If the sponsor, safety monitor and/or investigator's final determination of causality is "unknown but not related to the investigational device or other study treatments," this determination and the rationale for the determination will be documented in the respective subject's case history.

3.2.6 Stopping Rules

This study will be stopped prior to its completion if the intervention is associated with adverse effects that call into question the safety of the subjects as follows; (1) if there are 5 or more device related adverse events of severity greater than grade 4 on the CTAE scale; (2) if more than 20% of subjects (8 subjects) receiving SVF report an increase in pain to a level greater than eight (8) on the VAS pain scale or function decreases more than 50% compared to baseline functional assessment using the WOMAC function assessment subscale A3; (3) if escalation difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (4) any new information becomes available during the trial that necessitates stopping the trial. Any subject that has been treated prior to stopping the study for any reason will be monitored for adverse effects and if such events occur the subject will be treated until resolution.

3.2.7 Reporting adverse events to the FDA

For any observed or volunteered adverse event that is determined to be a UADE or any abnormal test findings, the investigator shall submit the event to the sponsor and FDA through the FDA's FDA Adverse Event Reporting System (FAERS).

A copy of this report will be provided to all participating study investigators.

The event will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the investigator first receives notice of the UADE and 30 days in the case of abnormal test findings

If, following receipt and investigation of follow-up information regarding an adverse event that was previously determined not to be a UADE, the sponsor, safety monitor and/or investigator determines that the event does meet the requirements for expedited reporting, the sponsor and/or investigator will submit the event to FAERS as soon as possible, but in no event later than 10 working days, after the determination is made.

Subsequent to the initial submission of a completed FAERS, the sponsor and/or investigator will submit additional information concerning the reported adverse event or abnormal test finding as requested by the FDA.

3.2.8 Reporting adverse events to the responsible IRB

For any adverse event determined to be a UADE or any abnormal test findings, the investigator will submit a copy of the FAERS report to the IRB as soon as possible and, in no event, later than 10 working days after the sponsor and/or investigator first receives notice of the UADE or 30 days for an abnormal test finding.

Follow-up information to reported adverse events and abnormal test findings will be submitted to the IRB as soon as the relevant information is available.

3.3 Withdrawal of subjects prior to completion of the study

Any subject that has been treated prior to withdrawal from the study for any reason will be monitored for adverse effects and if such events occur the subject will be treated until resolution and their medical outcome is determined.

4 DESCRIPTION OF THE INVESTIGATIONAL DEVICE

The GID SVF-2 device is a sterile single-use disposable canister used for harvesting, filtering, separating, and concentrating autologous stromal vascular fraction cells from adipose tissue for reintroduction to the same patient during a single surgical procedure for treatment of pain associated with joint osteoarthritis. The GID SVF-2 device is to be used only with the GID SVF Procedure Pack.

The GID SVF-2 device is a canister with various ports molded from polymer materials and a convenient tray. The canister is a closed system protecting the tissue aspirate through the harvesting process. The harvested tissue is deposited into the canister and filtered to capture the tissue and separate the fluid portion.

Functional Principle:

The harvested tissue and fluids are aspirated into a filter in the canister which captures the tissue particles and allows fluids through. The harvested tissue may be rinsed with a sterile LR solution injected through the Patient port or Luer port. A manual stirring assembly allows the user to mix the tissue and fluids during the filtering process. Waste fluids are transferred to a waste container that is in-line with the aspiration device.

5 MONITORING PROCEDURES

Monitoring for safety will be conducted by an independent safety monitor with the assistance of the PI and sponsor. A study monitor will monitor the study for compliance with the clinical protocol.

6 LABELING

The canister packaging is labeled for identity and an “Instructions for Use” and “User’s Manual” is provided with each unit.

The labeling will contain the statement "CAUTION - Investigational Device. Limited by Federal (or United States) Law to Investigational Use." [21 CFR 812.5(a)].

7 INFORMED CONSENT

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Sponsor and/or Investigator will prepare the informed consent form and HIPAA authorization and provide the documents to IRB for approval. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation (ICH) and will also comply with local regulations. The Sponsor and Investigator will retain an IRB-approved copy of the Informed Consent Form in the study master file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. A copy of the signed consent form will be given to the subject or legal representative of the subject and the original will be maintained with the subject’s study binder.

8 IRB INFORMATION

The protocol and consent form will be reviewed and approved by the applicable IRB of each participating center prior to study initiation. UADEs will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB’s written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB’s unconditional approval statement will be transmitted by the Investigator to the Sponsor prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

9 OTHER INSTITUTIONS

NA

10 ADDITIONAL RECORDS AND REPORTS

10.1 Data handling and record-keeping

All Case Report Forms will be completed for each subject enrolled into the clinical study. The investigator will review, approve and sign/date each completed CRF; the investigator’s signature serving as attestation of the investigator’s responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

Any missing, unused, or spurious data will be noted in the study records. All efforts will be made to account for missing data. Data may be removed if it does not meet quality criteria such as unreadable data or data entered with more than one value.

Source Data are the clinical findings and observations, laboratory and test data, and other information contained in *Source Documents*. *Source Documents* are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. When applicable, information recorded on the CRF shall match the Source Data recorded on the Source Documents.

10.2 Record maintenance and retention

The sponsor and investigator will maintain records in accordance with 21 CFR 812, Subpart G, to include:

Item	Sponsor	Investigator
FDA correspondence related to the IDE application and Investigational Plan; including copies of submitted Form FDA 3500A, supplemental IDE applications, current investigator lists, progress reports, notice of device recall or disposition,	X	

Item	Sponsor	Investigator
FDA notice of device recall or disposition, copies of submitted Form_FDA 3500A	X	X
IRB correspondence (including approval notifications) related to the clinical protocol; including copies of adverse event reports and annual or interim reports	X	X
Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s) and, if applicable, subject recruitment advertisements	X	X
Signed Investigator's Agreements and Certifications of Financial Interests of Clinical Investigators	X	X
Curriculum vitae (investigator and clinical protocol sub-investigators)	X	X
Certificates of required training (e.g., human subject protections, Good Clinical Practice, etc.) for sponsor and investigator and listed sub-investigators	X	X
Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol	X	X
Laboratory certification information	X	X
Instructions for on-site preparation and handling of the investigational device and/or study treatment or diagnostic product(s), and other study-related materials (i.e., if not addressed in the clinical protocol)	X	X
Master randomization list		X
Signed informed consent forms		X
Completed Case Report Forms, signed and dated by investigator		X
Source Documents or certified copies of Source Documents		X
Monitoring visit reports	X	X
Copies of sponsor and investigator correspondence to sub-investigators, including notifications of adverse effect information	X	X
Subject screening and enrollment logs		X
Subject Identification Log		X
Investigational device accountability records, including documentation of device disposal	X	X
Final clinical study report.	X	X

Staff at all facilities have training in GCP regulations, HIPAA and patient confidentiality.

During the study, patient data paperwork will be kept using standard patient records criteria, confidentiality and information security procedures that include limited access, Co-PI oversight of records and secured files. The data will be stored consistent with the clinics Records Retention Policies.

The subject will be assigned an anonymous, unique identifier called the Subject ID unrelated to the subject's name from a list of possible ID's. The subject's name and corresponding identifier will be recorded in a study look up document, which shall be kept at the study site consistent with confidential document policies.

The subject ID of excluded subjects will not be re-assigned. Information describing the reason(s) for exclusion will be documented on the Inclusion/Exclusion CRF.

CRFs will be labeled with the subject's Subject ID and no subject identifying information will appear on reports, publications, or other disclosures of clinical study outcomes.

The sponsor and investigator will retain the specified records and reports for up to two years after the marketing application is approved for the investigational device; or, if a marketing application is not submitted or approved for the investigational device, until two years after investigations under the IDE have been discontinued and the FDA so notified.

10.3 Data Management

The sites will send CRFs to the sponsor for data entry. CRFs may be sent via FedEx, fax or uploaded to the secure, HIPAA compliant share site. Data from the CRFs will be entered into a clinical data management system (CDMS) by the sponsor.

The data management system will have verifications and restrictions on data entry. The data entry will be 100% reviewed by an independent reviewer for accuracy. Erroneous, questionable or missing data will be collected on a Data Clarification Form (DCF) for each site and sent to the site for correction. The DCF will have an area for the site to make corrections or the site may make the correction on the original CRF and return to the sponsor.

Once all data has been entered, clarification and queries have been resolved, and the data is determined to be clean the database will be declared locked.

Appendix A – Schedule of Visits and Procedures

Case Report Form	Eligibility Screening	Pre-Surg.	Surg.	2 days ±24 hours Post-op	6 weeks (±1 week) Post-op	3 months (±2 weeks) Post-op	6 months (±2 weeks) Post-op	Safety 1 year (±1 month)	Safety 2 years (±1 month)	As Needed
Screening Form	X	X								
Inclusion/Exclusion		X								
MRI		X					X	X		
Demographics		X								
Vital Signs		X	X	X	X	X	X	X		
Surgery/Knee Injection CRF			X							
Cell Count Assay			X							
Cell Culture Assay			X							
Pain Evaluation (VAS)		X	X		X	X	X			
Short Form WOMAC		X	X		X	X	X			
Concomitant Medications		X	X	X	X	X	X			
Safety Follow-up								X	X	
Subject Exit									X	X
Adverse Events										X