16.1.1 Protocol and Amendments

1. Summary of Changes – Clinical Protocol
2. Protocol Version A, 21 August 2015
3. Protocol Version B, 24 November 2015

Summary of Changes Document – Clinical Protocol

In November 2015 the STYLE Clinical Trial Protocol—Rev A, August 21, 2015 was modified to Rev B, November 24, 2015. This document highlights the changes that were made in the revision.

1. **Blinding (Section 5.3)**: we adjusted the document to accurately reflect which parties are blinded and unblinded in carrying out the protocol. Given that a no-fat control is currently a group within the study and it is unfeasible to disguise this treatment relative to a fat containing arm, the sponsor, data management personnel (CRO), and study monitors will be aware of which treatment the subject received. It is imperative to note that the above parties have no potential impact in either the outcome or risk profile as core analysis (e.g., global and macrophotography) will remain conducted by blinded observers. It should also be noted that the statistician working to analyze the data will also remain blinded.

2. **Questionnaires (Sections 8, 9.6, & Appendix A):** we adjusted the protocol to remove inconsistencies with the timing of both investigator and subject questionnaires. Both of these questionnaires (attached in the correspondence) are not relevant for any pre-procedure assessment as they reflect perceived changes subsequent to the intervention. As such, the sections of the document reflecting this timing have been amended accordingly. This change has no potential impact in either the outcome assessment or risk profile of the protocol.

3. **Timing of visit (Sections 9.1 & Appendix A):** the original protocol called for acquisition of both global and macrophotography at Day -1. In the course of working with the approved vendor (Canfield Scientific), it became evident that this time period would not allow adequate time to monitor for the quality of the images obtained. As such, we are proposing that both global and macro photography is acquired at least one month and no later than one week prior to the scheduled intervention to allow for this critical quality assessment. With this change, we are eliminating one round of global photography. This change has no potential impact in either the outcome assessment or risk profile of the protocol.

Subcutaneous Transplantation of Autologous Cell Enriched Adipose Tissue For Follicular Niche Stimulation in EarlY Stage ALopEcia Androgenetica (STYLE): a Randomized, Blinded, Controlled Trial

STYLE Clinical Trial

Version A

21August2015

NCT number: NCT02503852

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STYLE TRIAL PROTOCOL APPROVAL FORM

Study Title:	Subcutaneous Transplantation of Autologous Cell Enriched Adipose Tissue For Follicular Niche Stimulation in EarlY Stage ALopEcia Androgenetica (STYLE): a Randomized, Blinded, Controlled Trial
Short Title:	STYLE Trial
Protocol Version A Date:	21 August 2015

This study protocol was subjected to critical review. The information it contains is consistent with the sponsor's current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, as amended in 2013, Good Clinical Practice (GCP) Consolidated Guidance in guidelines of the International Conference on Harmonization (ICH) E2 & E6, and 21CFR 11, 50, 54, 56, 812, 814 and 820. The study will also be carried out in keeping with all applicable laws, rules, and regulations.

Eric Daniels Chief Medical Officer Kerastem Technologies, LLC	Date (dd/mmm/yyyy)

INVESTIGATOR STATEMENT PAGE

Study Sponsor: **Kerastem Technologies, LLC**
Clinical Trial: **STYLE Trial**
Protocol Version A: 21August2015

Study Title: Subcutaneous Transplantation of Autologous Cell Enriched Adipose Tissue For Follicular Niche Stimulation in EarlY Stage ALopEcia Androgenetica (STYLE): a Randomized, Blinded, Controlled Trial

The information contained in this document and all information provided to you related to this protocol are the confidential and proprietary information of Kerastem (Sponsor) and except as may be required by federal, state or local laws or regulations, may not be disclosed to others without prior written permission of Sponsor. The Principal Investigator at each site may, however, disclose such information to supervised individuals working on the protocol, provided such individuals agree to be bound to maintain the confidentiality of such protocol information.

I agree to abide by the statement of confidentiality.

I agree to provide my curriculum vitae.

I agree to disclose if I was involved in an investigation or other research that was terminated, and an explanation of the circumstances that led to termination

I agree to conduct the study according to this protocol. Any changes in procedure will only be made if necessary to protect the safety, rights, or welfare of patients.

I agree to comply with the current ICH, GCP and CFR Guidelines.

I agree to conduct the study in person or to supervise the study.

I agree to ensure that all who assist me in the conduct of the study have access to the study protocol and any amendments and are aware of their obligations.

As an investigator for the STYLE Trial, I intend to commit to conducting the investigation in accordance with the investigator agreement, the investigational plan, Part 812 and other applicable FDA regulations and conditions of approval imposed by the reviewing IRB and FDA. I agree to supervise all testing of the device involving human subjects and will ensure that the requirements for obtaining informed consent are met. As an investigator, I am committed to provide sufficient and accurate financial disclosure information and update information if any

relevant changes occur during the investigation and for one year following the completion of the study.

Principal Investigator (Print Name and Title)

Principal Investigator (Signature) Date (dd/mmm/yyyy)

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STYLE TRIAL - PROTOCOL SUMMARY

Title	Subcutaneous Transplantation of Autologous Cell Enriched Adipose Tissue For Follicular Niche Stimulation in EarlY Stage ALopEcia Androgenetica (STYLE): a Randomized, Blinded, Controlled Trial
Test Products	Celution® System (Celution Device, Celution Consumable Set and Celase) used for processing of Autologous Adipose Derived Regenerative Cells (ADRCs) combined with adipose tissue processed and purified with Puregraft® 50 System
Objective	The primary objective of this study is to evaluate the safety and feasibility of the Celution and Puregraft Systems in the processing and preparation of an autologous fat graft enriched with adipose-derived regenerative cells (ADRCs) in the treatment of early alopecia androgenetica.
Design	Prospective, Randomized, Controlled Safety and Feasibility Trial
Sample Size	70 patients (40 ADRC + adipose, 20 fat only control, 10 no-fat control)
Study Location	Up to (8) sites in the United States
Indication	Androgenic Alopecia (Androgenetica Alopecia, AGA)
Visit Schedule	Screening (Day -28 to Day -1), Procedure Day (Day 1), and follow up visits at weeks 1, 6, 12, 24 and 52 weeks
Treatment Arms	Subjects will be randomized 2:2:2:1 to receive either 0.1ml/cm^2 scalp of autologous fat enriched with 0.5 x 10^6 ADRC/cm^2 scalp (n=20), 0.1 ml/cm^2 scalp of autologous fat enriched with 1.0 x 10^6 ADRCs/cm^2 scalp (n = 20), 0.1ml/cm^2 scalp of autologous fat enriched with a matching saline control (fat alone control; n=20), or 0.1 ml/cm^2 scalp of saline enriched with a matching dose of saline (no-fat control; n=10). In each subject, 40 square centimeters of scalp will be treated. The study treatment will be delivered in the subcutaneous adipose layer of the scalp in via two separate injections – one of either 0.1ml/cm^2 scalp of adipose or saline followed by a second injection of ADRCs or saline per square centimeter of scalp.
Primary Endpoint	Safety & tolerability through 24 weeks
Secondary Endpoints	• Trichograms (Hair Growth) at 24 weeks • Trichograms (Hair Density)at 24 weeks • Global photographs to assess scalp coverage at 24 weeks

	• Hair Investigator Satisfaction Survey at 24 weeks
Exploratory Endpoints	• Trichograms (Hair Growth)at times other than 24 weeks • Trichograms (Hair Density) at times other than 24 weeks. • Trichograms (Hair Thickness) at times other than 24 weeks • Global photographs to assess scalp coverage other than 24 weeks • Hair Investigator Satisfaction Survey at times other than 24 weeks.
Safety Endpoints	Adverse events, Serious Adverse Events, UADEs
Inclusion & Exclusion Criteria	**Inclusion Criteria** 1. Males with a diagnosis of Alopecia Androgenetica 2. Females with a diagnosis of Alopecia Androgenetica 3. Males with hair loss consistent with Grades III, IIIA, III-Vertex, IV, IV-A, based on Norwood-Hamilton Scale (Figure 1) 4. Females with hair loss consistent with Grades I-3, I-4, II-1, II-2 based on the Savin Scale (Figure 2) 5. Provide written informed consent and comply with the study requirements 6. For women of childbearing potential: Negative pregnancy test at screening visit plus subject agrees to maintain two forms of contraception for the duration of the study. 7. Subject is willing to maintain a consistent hair length and natural hair color, without the use of any coloring agents, during the study period. 8. Ability to complete study procedures, patient surveys, and pictures. 9. Subject is ≥ 18 years of age. 10. Body Mass Index < 40kg/m^2 **Exclusion Criteria** 1. Subjects who have used minoxidil, or any oral or topical medication including over the counter and herbal medications for the treatment of hair loss within 6 months of study screening, or finasteride or dutasteride within 12 months of study screening 2. Treatment with an investigational product or procedure within 30 days or plans to participate in another clinical study 3. Subject who has previously failed or has been deemed non-responsive to a previous experimental hair loss treatment. 4. Subject must have no previous hair transplant, cell treatment, micro needling, or any other treatment in the last 6 months in the scalp. 5. Subject is currently suffering from an active autoimmune disease such as serum lupus erythematosus, or alopecia areata. Subject is currently suffering from dermatologic condition in the treatment area or has a significant scar in the hair treatment area that, in the opinion of the investigator, will make hair growth difficult (such as systemic burns,

	etc.). 6. History of autoimmune disease or organ transplantation or a patient on immunosuppressive medication(s). 7. Diagnosis of cancer, receiving active treatment 8. Active systemic infection 9. Requires chronic antibiotics, systemic corticosteroids 10. Use of systemic agents that increase bleeding or clotting, or disorders associated with these effects, including patients receiving GIIB/IIIa inhibitors within 2 weeks prior to the study procedure through to 1 week after the study procedure. 11. Clinically significant medical or psychiatric illness currently or within 30 days of study screening as determined by the investigator 12. Prior surgery in the treatment area 13. Any disease or condition (medical or surgical) that, in the opinion of the investigator, might compromise dermatologic, hematologic, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, or central nervous system function; or any condition that would place the subject at increased risk 14. Pregnant or lactating women or women trying to become pregnant 15. Known allergic reaction to components of study treatment and/or study injection procedure 16. Subject has any disorder that may prevent compliance to study procedures and visits 17. Subject who is part of the study staff, a family member or friend 18. Diabetes or thyroid disorder 19. Subject who has a sensitive, irritated, or abraded scalp area. 20. Women who have an alternate diagnosis that is associated with hair loss. 21. Body Mass Index < 18kg/m^2 22. Clinically significant abnormal findings on laboratory screening panels, including hemoglobin ≤ 10 g/dL. 23. Hepatic dysfunction, as defined as aspartate aminotransferase (AST), alanine aminotransferase (ALT), or bilirubin levels > 1.5 times the upper limit of normal range (x ULN) prior to randomization. 24. Chronic renal insufficiency as defined as a serum creatinine > 1.5 mg/dL in men or > 1.2 mg/dL in women. 25. An elevated PT/PTT, INR, or platelet count < 100 x 10^9/L

ABBREVIATIONS

ADL	Activities of Daily Living
AGA	Androgenic Alopecia
ADRC	Adipose-Derived Regenerative Cells
AE	Adverse Event
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
AFT	Autologous Fat Transfer
CFU-F	Colony Forming Units Fibroblast
CFR	Code of Federal Regulations
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ET	Early Termination
FPHL	Female Pattern Hair Loss
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ID	Identification
IFU	Instructions for Use
IV	Intravenous
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MPHL	Male Pattern Hair Loss
PI	Principal Investigator
pRBC	Pack Red Blood Cells
PTE	Per Treatment Evaluation
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
WBC	White Blood Cell

1 OBJECTIVE

The primary objective of this study is to evaluate the safety and efficacy of the Cytori Celution and Puregraft Systems in the processing and preparation of an autologous fat graft enriched with adipose-derived regenerative cells (ADRCs) in the treatment of early alopecia androgenetica.

2 BACKGROUND

2.1 Alopecia Androgenetica

Alopecia Androgenetica (AGA) is the most common form of both male pattern hair loss (MPHL) and female pattern hair loss (FPHL)[1,2] with the condition affecting approximately 50% of the male population and less than 45% of women going through life with a full head of hair. The degree of hair loss in the male patient is generally classified using the Norwood Hamilton Classification (Figure 1) and FPHL is evaluated based on the Savin scale (Figure 2)[1,3]. The incidence and prevalence of the condition are generally well documented in both genders. Stough and co-workers reported that in White males, 30% have AGA by age 30 and 50% by age 50 with lower incidences seen in African American, Chinese, and Japanese populations[3]. In a population based report looking at MPHL, the authors reported that in the 30-35 years age group, grade I hair loss was 51%, while grade II was 43% and grade VI was only approximately 19%--clearly highlighting early hair loss in the younger population[4]. Of the 1,005 men in the study aging from 30-50 years, 44% were found to have grades I-III hair loss.

In women, diffuse thinning and loss of hair density with maintenance of the frontal hairline describe the typical pattern of loss5. In one report, the prevalence of early, clinically detectable FPHL was 12% of females between 20-29 years of age and 25% by 49 years of age[2]. In the table presented below (Table 1), Gan and Sinclair documented the distribution of hair loss in 752 women using a modified 5-point grading scale[6]. Below the age of 40 years, 99% of women reporting loss documented early stage loss.

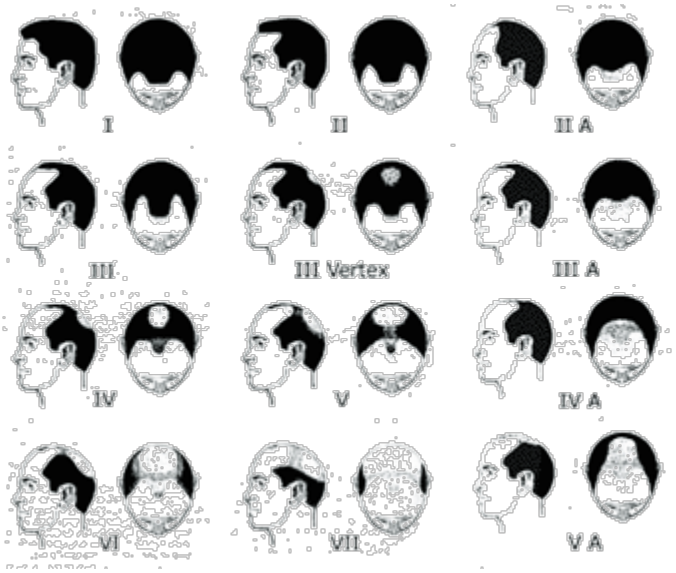
TableIV. Hair patterns in female subjects

	Hair thickness						
Age	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Total	1–stage 1
5–9	72 (100%)						–
20–29	50 (88%)	5 (9%)	1 (2%)	1 (2%)		57	7 (12.3%)
30–39	73 (83%)	14 (16%)		1 (1%)		88	15 (17.0%)
40–49	91 (75%)	28 (23%)		3 (2%)		122	31 (25.4%)
50–59	106 (72%)	29 (20%)	11 (7%)	1 (1%)		147	41 (27.9%)
60–69	73 (59%)	37 (30%)	11 (9%)	2 (2%)	1 (1%)	124	51 (41.1%)
70–79	58 (46%)	35 (28%)	24 (19%)	6 (5%)	2 (2%)	125	67 (53.6%)
≥ 80	23 (43%)	15 (28%)	8 (15%)	8 (15%)		54	35 (57.4%)
Total	474 (66%)	163 (23%)	55 (8%)	22 (3%)	3 (0.4%)	717	247 (32.2%[a])

[a]Adjusted to age.

In sum, a significant percentage of both male and female population suffer from AG at a relatively early age.

Figure 1—MPHL Norwood Hamilton Classification



Class I represents an adolescent or juvenile hairline and it not actually balding. The adolescent hairline generally rests on the upper brow crease.

Class II indicates a progression to the adult or mature hairline which sits a finger breath (1.5cm) above the upper brow crease, with some temporal recession. This also does not represent balding.

Class III is the earliest stage of male hair loss. It is characterized by a deepening temporal recession.

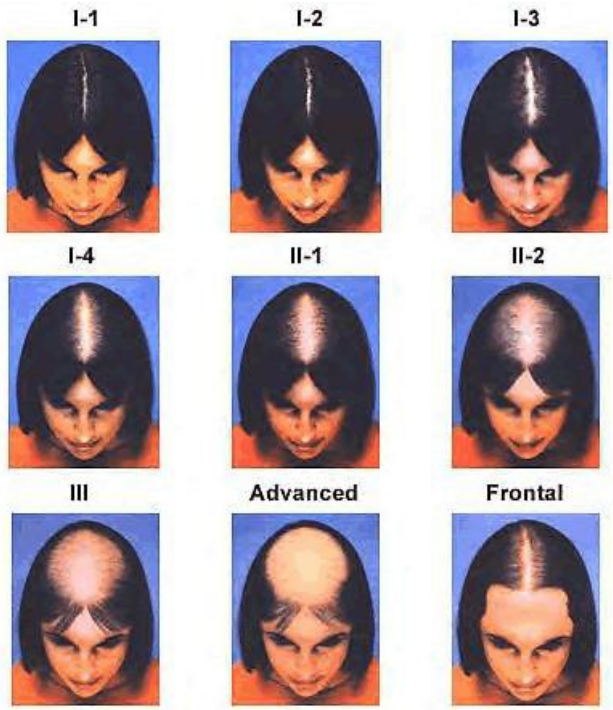
Class III Vertex represents early hair loss in the crown (vertex).

Class IV Is characterized by further frontal hair loss and enlargement of vertex, but there is still a solid band of hair across top separating front and vertex.

Class V the bald areas in the front and crown continue to enlarge and the bridge of hair separating the two areas begins to break down.

Class VI occurs when the connecting bridge of hair disappears leaving a single large bald area on the front and top of the scalp. The hair on the sides of the scalp remains relatively high.

Figure 2—FPHL Ludwig Scale



The current treatment regimen for alopecia androgenetica is a spectrum ranging from non-invasive medicinal approaches to robot-assisted surgical transplantation of thousands of follicular units. On the non-invasive side, the two medicines currently approved for treatment of genetic pattern alopecia by the FDA are finasteride (for men only) and minoxidil[8,9]. Both of these medicines carry untoward side-effects. For finasteride, sexual dysfunction, particularly for the younger patient who is most likely to present with early hair loss, was seen in between 2.1% and 3.8% of men[10]. Initial treatment of early alopecia is typically non-invasive and the two medications approved by the FDA today are minoxidil and finasteride. For minoxidil, it is reported that approximately one-third of patients with AA respond with new hair growth[11]. In contrast, invasive transplant options are generally not offered to patients with early AA and if so, require significant financial resources. As a result, there remains a significantly large gap between these medicinal and transplant options. Hence a distinct medical need remains specific to addressing early alopecia.

During hair follicle growth (anagen), the hair follicle delves deep into the rich dermal macroenvironment as it grows to maturity where it is surrounded by large lipid-filled adipocytes. These intradermal adipocytes regenerate with faster kinetics than other adipose tissue depots and such growth parallels with the hair cycle, suggesting an interplay exists between hair follicle cells and adipocytes[12]. Thus, it has been established that adipose is an integral part of the normal hair cycle and it is hypothesized that telogen may be due to an absence of adipose tissue as it is reported that hair loss and decreased adipocytes occur together[12,13]. Therefore, the transplantation of adipose tissue, or autologous fat transfer (AFT), into the subcutaneous layer of fat in the scalp for purposes of stimulating hair growth is consistent with the reported literature that indicates hair loss and adipose loss occur in tandem.

Autologous Fat Transfer

In an AFT procedure, a patient's subcutaneous adipose tissue is aspirated from one location (most commonly the abdomen or thighs) and transferred into another depot of subcutaneous fat located throughout the body (e.g., mid-face). This procedure is reported to be practiced by physicians for over 100 years and autologous fat should be free from problems often associated with artificial materials or from allergic reactions[14]. However, AFT is not without its own limitations most significant of which is the fact that an unpredictable amount of the transferred fat can die as a result of damage during tissue harvest, processing, and implantation leading to loss of volume and a degree of unpredictability in outcome.

The process of fat transfer necessarily involves disconnecting the fat from its blood supply, implanting it into the defect, and then waiting for natural healing processes to incorporate the transferred tissue with native fat. Survival of the transferred tissue is dependent upon harvest and processing approaches that maximize tissue viability[15]. It is also dependent upon simple diffusion to supply nutrients and oxygen and to remove wastes until such time as healing processes restore its blood supply. Diffusion through a solid tissue such as fat is only effective across a distance of a few millimeters. Consequently, any transferred tissue that is more than a few millimeters away from the blood supply of recipient site tissue is at risk of dying. Loss of graft tissue from this problem is a frequent problem. Clinicians frequently overcorrect adding extra tissue in an effort to compensate for inevitable tissue loss that has been estimated at between 20-80% of the implanted tissue[16-18]. As a result of this unpredictability defect repair frequently requires multiple repeated or staged procedures performed at intervals of three or more months. For example, one large study reports up to five treatments needed (mean = three treatments) in order to achieve success in restoring volume[19]. This leads to delays in achievement of effective treatment of the defect, expense, and the higher morbidity of repeated tissue collection and implantation.

A number of investigators have evaluated ways by which the healing process can be modulated in an effort to understand and augment graft retention and, thereby, limit the number of procedures needed to achieve successful treatment. For example, animal studies have shown that use of agents that stimulate the healing process (for example, gene therapy with factors that stimulate new blood vessel growth[20]) can increase the survival of transferred tissue and that, conversely, agents that inhibit healing reduce survival[21]. Recent preclinical and clinical data have shown in addition to being a source of tissue for soft tissue filling, human adipose tissue contains cells that have the ability to promote healing[22,23]. Zhu *et al* have used an animal model to show that coating one volume of adipose tissue with cells isolated from another volume of adipose tissue results in an approximate doubling of graft retention at six and nine months[24]. This finding has been confirmed by an independent study[25]. The concept of this approach is that signals generated at the interface between implanted fat and adjacent breast fat will induce improved healing. Increasing the number of cells capable of generating these signals at this interface will lead to successful tissue retention.

In addition, Puregraft processed adipose has an excellent safety profile in aesthetic body contouring[26].

Currently, there are few, if any, minimally invasive, autologous cell therapeutic modalities being developed that address early alopecia. However, analyses from other therapeutic applications of

ADRCs and AFT suggest that a cell-enriched based approach for the treatment of early alopecia may be of significant benefit.

2.1.1 Clinical Experience with ADRCs

To date, thousands of patients have been treated with autologous ADRCs isolated using the Celution System (Cytori Therapeutics, San Diego, USA). Celution processed ADRCs have an excellent safety profile in a variety of conditions including acute myocardial injury, patients with chronic heart muscle damage, breast insufficiency following lumpectomy (a cell-enriched AFT procedure), chronic cutaneous wounds, and urinary incontinence, and most recently in a small study of scleroderma patients[27-32].

In addition, Puregraft processed adipose has an excellent safety profile in aesthetic body contouring[26].

Cytori's initial clinical experience in treating pathological conditions was in the myocardium, The PRECISE Clinical Trial evaluated the safety and feasibility of intramyocardial administration of ADRCs in patients with chronic myocardial ischemia not amenable to revascularization.[27] Clinical results at 18 months have demonstrated safety and signs of feasibility. PRECISE was a prospective, double-blind, randomized, parallel group, placebo-controlled, sequential dose escalation study which enrolled 27 subjects. Following baseline electromechanical mapping, subjects received ≤ 15 intramyocardial injections of ADRCs (n=21; median dose of ADRCs 42 x 10^6 per subject) or placebo (n=6: indistinguishable solution) in the area(s) of the heart with inducible ischemia. ADRCs were processed using the Cytori Celution System. ADRC-treated subjects demonstrated improvement in maximum oxygen consumption (VO_2max) relative to a placebo control. Adverse events and serious adverse events were equally distributed across all treatments groups with angina reported as the most frequent SAE.

The APOLLO Clinical Trial was a safety and feasibility study of ADRCs processed by the Celution System and delivered via the intracoronary route in the treatment of patients with ST-segment elevation myocardial infarction (STEMI).[28] This was a prospective, double-blind, 3:1 randomized (ADRC: Placebo), parallel group, placebo-controlled trial. A total of 14 patients were enrolled and treated according to protocol, 10 patients received ADRCs and four received placebo.

The APOLLO study demonstrated that liposuction adipose harvest for the purpose of processing and returning autologous ADRCs via the intracoronary infusion of 20 x 10^6 ADRCs can be performed with an acceptable safety profile.

Case series have described benefits in the treatment of radiation injury, fistulas and stress urinary incontinence. Yoshimoto et al. described efficacy of ADRC treatment in three patients presenting with chronic radiation injuries with ulcers and severe fibrosis.[29] They reported increases in local blood circulation at the site by ultrasound and dramatic wound healing. Gotoh et al recently described improvements in urinary incontinence following ADRC injections in a case series of 11 men who underwent radical prostatectomy.[30] Of note, enhanced ultrasonography showed a progressive increase in blood flow to the injected area in all patients. Borowski reported complete wound closure of three patients treated for long-standing cryptoglandular fistula-in-ano

using ADRCs.[31]An open label trial in 12 patients with systemic scleroderma from France examining the effects of subcutaneous administration of ADRCs to all fingers has recently been published.[32] Data at six months indicated significant improvements in Cochin score, Raynaud's severity score, and in the Scleroderma Health Assessment Questionnaire (SHAQ). The procedure was tolerated well without complications.

3 RATIONALE

For both sexes, the negative physical and psychological effects of AGA have been documented. In Stough's report, the authors indicate that while the condition may not appear to cause direct physical harm in men, hair loss can protect against sunburn, cold temperatures, mechanical injury, and ultraviolet light[3]. Beyond the physical, hair loss is known to psychologically affect the balding individual's perceptions of themselves. This is particularly true when looking at FPHL, where Cash and co-workers reported that while AA was a stressful experience for both sexes, it was substantially more distressing for women[7]. In sum, the impact of the condition should not be relegated as simply aesthetic in nature, and therefore satisfactory treatment regimens are necessary.

4 STUDY DESIGN

The STYLE Trial is a prospective, randomized, multi-center device trial intended to evaluate the safety and efficacy of the Celution and Puregraft Systems in the processing and preparation of an autologous fat graft enriched with adipose-derived regenerative cells (ADRCs) in the treatment of early alopecia androgenetica. Patients may be included if they are undergoing an elective cosmetic liposuction. Following informed consent and screening evaluations, eligible subjects will undergo pre-operative testing. Subjects will then undergo a fat harvest using local anesthesia with or without conscious sedating. Subjects will be randomly assigned to receive a fat graft cell enriched with ADRCs (available in two different doses), a fat graft without cell enrichment using a visually-matched blood saline solution (fat alone control), or a saline injection (no-fat control) in a 2:2:2:1 ratio.

While undergoing liposuction, lipoaspirate will be processed in the Puregraft System to remove the lipoaspirate of impurities and in the Celution System to isolate and concentrate ADRCs. After the liposuction is completed), patients will have, under a ring block local anesthesia (see further description below), a subcutaneous scalp injection of either Puregraft purified autologous fat or saline (no-fat control) followed by a separate second injection, of either ADRCs (available in two different doses), a visually-matched blood saline solution (fat alone control), or saline (no-fat control) in a 2:2:2:1 ratio.

All subjects will undergo clinical evaluations and laboratory testing prior to and after the procedure as outlined in *Section 9.0, Study Assessments,* and in the *Schedule of Procedures (Appendix A).*

4.1 Study Population

Subjects with documented early stage alopecia androgenetica will be evaluated for this study.

4.2 Sample Size

The STYLE Clinical Trial will have a sample size of 70 patients.

4.3 Clinical Sites

Up to eight (8) clinical centers in the United States will be selected to participate in the STYLE Clinical Trial.

4.4 Study Duration

Enrollment of subjects will occur over approximately 6 months. For each patient, the study duration will include a screening period of up to 28 days and a 52 week follow-up period. Therefore, the study duration is estimated to be 18 months.

4.5 Study Endpoints

4.5.1 Primary Endpoint

Safety & tolerability throughout 24 weeks

4.5.2 Secondary Endpoints

1. Trichograms (Hair Growth)t 24 weeks (change from baseline)
2. Trichograms (Hair Density) at 24 weeks (change from baseline)
3. Global photographs at 24 weeks (change from baseline)
4. Hair Investigator Satisfaction Survey at 24 weeks (change from baseline)

4.5.3 Exploratory Endpoints

1. Trichograms (Hair Growth)at times other than 24 weeks
2. Trichograms (Hair Density) at times other than 24 weeks
3. Trichograms (Anagen/Telogen Rate, Hair Thickness) at times other than 24 weeks
4. Global photographs other than 24 weeks
5. Hair Investigator Satisfaction Survey at times other than 24 weeks

4.5.4 Safety Endpoints

Adverse events, Serious Adverse Events, and UADEs

4.6 Inclusion Criteria

Subjects will be enrolled into this study only if they meet ALL of the following criteria:

1. Males with a diagnosis of Alopecia Androgenetica
2. Females with a diagnosis of Alopecia Androgenetica

3. Males with hair loss consistent with Grades III, IIIA, III-Vertex, IV, IV-A, based on Norwood-Hamilton Scale (Figure 1)
4. Females with hair loss consistent with Grades I-3, I-4, II-1, II-2 based on the Savin Scale (Figure 2)
5. Provide written informed consent and comply with the study requirements
6. For women of childbearing potential: Negative pregnancy test at screening visit plus willingness to maintain two forms of contraception for the duration of the study.
7. Subject is willing to maintain a consistent hair length and natural hair color, including the absence of coloring agents, during the study period.
8. Ability to complete study procedures, patient surveys, and pictures.
9. Subject is ≥ 18 years of age.
10. Body Mass Index < 40kg/m^2

4.7 Exclusion Criteria

Subjects will not be enrolled into this study if they meet ANY of the following criteria:

1. Subjects who have used minoxidil, or any oral or topical medication including over the counter and herbal medications for the treatment of hair loss within 6 months of study screening, or finasteride or dutasteride within 12 months of study screening
2. Treatment with an investigational product or procedure within 30 days or plans to participate in another clinical study
3. Subject who has previously failed or has been deemed non-responsive to a previous experimental hair loss treatment.
4. Subject must have no previous hair transplant, cell treatment, micro needling, or any other treatment in the last 6 months in the scalp.
5. Subject is currently suffering from an active autoimmune disease such as serum lupus erythematosus, or alopecia areata. Subject is currently suffering from dermatologic condition in the treatment area or has a significant scar in the hair treatment area that, in the opinion of the investigator, will make hair growth difficult (such as systemic burns, etc.).
6. History of autoimmune disease or organ transplantation or a patient on immunosuppressive medication(s).
7. Diagnosis of cancer, receiving active treatment
8. Active systemic infection
9. Requires chronic antibiotics, systemic corticosteroids
10. Use of systemic agents that increase bleeding or clotting, or disorders associated with these effects, including patients receiving GIIB/IIIa inhibitors within 2 weeks prior to the study procedure through to 1 week after the study procedure.
11. Clinically significant medical or psychiatric illness currently or within 30 days of study screening as determined by the investigator
12. Prior surgery in the treatment area
13. Any disease or condition (medical or surgical) that, in the opinion of the investigator, might compromise dermatologic, hematologic, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, or central nervous system function; or any condition that would place the subject at increased risk
14. Pregnant or lactating women or women trying to become pregnant

15. Known allergic reaction to components of study treatment and/or study injection procedure
16. Subject has any disorder that may prevent compliance to study procedures and visits
17. Subject who is part of the study staff, a family member or friend
18. Diabetes or thyroid disorder
19. Subject who has a sensitive, irritated, or abraded scalp area.
20. Women who have an alternate diagnosis that is associated with hair loss.
21. Body Mass Index < 18 kg/m^2
22. Clinically significant abnormal findings on laboratory screening panels, including hemoglobin ≤ 10 g/dL.
23. Hepatic dysfunction, as defined as aspartate aminotransferase (AST), alanine aminotransferase (ALT), or bilirubin levels > 1.5 times the upper limit of normal range (x ULN) prior to randomization.
24. Chronic renal insufficiency as defined as a serum creatinine > 1.5 mg/dL in men or > 1.2 mg/dL in women.
25. An elevated PT/PTT, INR, or platelet count < 100 x 10^9/L

5 ENROLLMENT

5.1 Subject Enrollment

Patients are considered enrolled in this study when all of the following have occurred:

1. Written informed consent is obtained
2. All inclusion criteria and no exclusion criteria have been met
3. All screening evaluations are complete

5.2 Randomization and Subject Identification

All subjects will undergo liposuction and will be randomized into one of four parallel arms in a 2:2:2:1 ratio to receive either low dose ADRCs cell enriched fat (n=20), high dose ADRC cell enriched fat (n=20), non-cell enriched autologous fat alone control (n=20), or no-fat control saline injections (n=10). Randomization will be via an interactive voice/web response system (IVRS/IWRS), or an alternatively acceptable system, and occur on the procedure day, prior to the start of liposuction.

Patients randomized into the study will be assigned the treatment corresponding to the next available number in the computer-generated randomization schedule. The dose of the test material (ADRCs or placebo) is discussed in Section 6.3.

Randomization and dose preparation will be performed by an unblinded pharmacist, or other designated qualified personnel, as outlined in the Study Reference Manual. The unblinded pharmacist or designee will not be involved in study patient care, management or follow up procedures and assessments.

5.3 Blinding Procedures and Safeguards

The following will be the "blinded parties", meaning that the listed will have no knowledge of the patient's treatment assignment:

- Patients
- Core Laboratories
- Data Management personnel
- Sponsor
- Study Monitors

The "**unblinded parties**", meaning those that will or may have knowledge of a patient's treatment assignment, will be the following:-

- Investigators
- Unblinded Pharmacist or designee involved in the dose preparation procedures and randomization of the patient
- Data Monitoring Committee Members
- Unblinded Statistician

The study blind should not be broken except in a medical emergency (where knowledge of the test material received would affect the treatment of the emergency) or regulatory requirement (e.g., for SAEs or death).

If unblinding becomes necessary, the Investigator should notify the Sponsor or the Medical Monitor as soon as possible. If the blind is broken, the date, time and reason must be recorded in the Subject's electronic case report form (eCRF), together with a note of a protocol violation if applicable, and any applicable reports [e.g. Adverse Event (AE)].

5.4 Subject Withdrawal and Replacement

Subjects may withdraw from the study at any time and for any reason without penalty or prejudice to his or her future medical care. If a subject is prematurely withdrawn from the study for any reason, the reason(s) for withdrawal must be recorded in the Subject's source documentation and on the eCRF.

The Investigator must make every effort to perform the Early Termination evaluations. This visit shall take place as soon as possible after it is determined that the Subject will be withdrawn from the study and will comprise the observations and procedures scheduled at the next visit.

6 CELUTION & PUREGRAFT SYSTEMS

6.1 Celution& Puregraft System Descriptions

The Celution System consists of a stand-alone re-useable hardware unit called the Celution Device, the Celution Consumable Set, and Celase®. The Celution System prepares an ADRC output from adipose tissue collected by standard liposuction techniques.

Following the collection of tissue, the adipose tissue is introduced into the device's collection canister in order to wash the adipose tissue and remove deleterious substances (such as cellular debris)(Detailed instructions for use are found in the *Celution User Manual, the Celution Consumable IFU and the Celase IFU*).

The Puregraft 50 System is a sterile, single use, closed system intended for the preparation and delivery of autologous fat grafts back to the same patient for cosmetic and reconstructive surgery applications. The dual filtration bag system utilizes its swabable luer activated valves to connect to an off-the-shelf sterile luer lock syringe and its attached slider is used to facilitate the movement of liquids through the filter mesh and out of the Puregraft bag through the drain stub as waste. Detailed instructions for use are found in the Puregraft IFU).

6.2 Device Characterization and Intended Use

In combination with the Puregraft 50 System, the Celution System (Celution Device, Celution Consumables Set, and Celase reagent) is intended to digest adipose tissue in order to further extract, wash and concentrate adipose derived regenerative cells (ADRCs) intended for combination with autologous fat and reimplantation subcutaneously into the scalp for investigational use in the STYLE clinical trial.

The Puregraft 50 System is intended to process and purify adipose tissue to be combined with concentrated stromal stem cells and other associated progenitor cells intended for autologous implantation subcutaneously into the scalp for investigational use in the STYLE clinical trial.

6.3 Contraindications

1. Non-autologous use is contraindicated
2. Use of any tissues other than adipose is contraindicated

6.4 Intended Clinical Performance

The Celution System is designed to process lipoaspirated tissue and separate ADRCs from adipose tissue by enzymatic disassociation of the tissue and using buoyancy differences to separate the ADRCs from lipid containing adipocytes at the point of care. When ADRCs are prepared using the Celution System, the resultant cell suspension contains all of the components naturally occurring in the native tissue. Preparation of autologous ADRCs for subcutaneous delivery using the Celution System involves no cell culture and can be prepared and re-implanted into the same patient within three hours from completion of lipoaspiration.

The total viable cell count and percentage viability for each sample will be used as the acceptance criteria. This will be assessed for each patient to decide whether the cell output is acceptable, and to prepare the prescribed dose. The viable cell count will be performed by the commercially available NucleoCounter® Automated Cell Counting System. Using a small sample of the Celution System output, the NucleoCounter Automated Cell Counting System provides a count of both live and dead nucleated cells in the total sample. All personnel involved will be trained according to standardized procedures and work instructions. Cytori has performed characterizations of the live cell output obtained by the Celution System and this is consistently 70% viability or greater. This sample count is used to calculate the total number of live nucleated cells from the total preparation, to arrive at percentage of viable cells that are available for introduction into the patient.

The Puregraft System is designed to prepare purified lipoaspirate. This purification involves the near complete removal of free lipid, RBCs, and WBCs. All personnel involved will be trained according to standardized procedures and work instructions.

6.5 Celution& Puregraft System Output; Physical, Chemical, and Pharmaceutical Properties of ADRCs

The output of the Celution System is an ADRC output obtained from autologous lipoaspirate tissue. The suspension of viable ADRCs has been characterized with an average viability of >70% and the average yield is $3.24 \times 10^5 \pm 1.48$ of mononuclear cells per gram of adipose tissue entered into the Celution System. An index of regenerative cell potential, the CFU-F assay, shows that 1.51% of those ADRCs form colonies (mean range of 0.13 to 4.08% colony forming units).

The product is a suspension of cells in a diluent. The cellular components of the suspension are made up of nucleated and non-nucleated cells. The non-nucleated cells are red blood cells (RBC) that comprise > 95% of the total cell suspension. The nucleated cells make up approximately 0.1 – 5% of the total cell suspension. Nucleated cells are present in the following approximate minimum percentages: CD 31^+, CD 34^+ (> 2%); CD 34^+, CD 31^-, CD 45^- (> 10%); CD 45+, CD 31-, CD 34- (> 15%). The combination of these three phenotypes will account for greater than 90% of nucleated cells in the product. Table 1 summarizes the ADRC cellular suspension processed by the Celution System.

Table 1. ADRC cellular suspension components and concentrations

Cell Type	Phenotype	Relative Identity of Nucleated Cell Population	% of total cell suspension
Non-nucleated Cells	Red Blood Cells		> 95%
Nucleated Cells	CD 31+, CD 34+	> 2%	0.1-5%
	CD 34+, CD 31-, CD 45-	> 10%	
	CD 45+, CD 31-, CD 34-	> 15%	

Puregraft 50 System

The Puregraft 50 System is used in conjunction with a lipoplasty device (user supplied) and does not contact the patient as it does not connect to vacuum. The Puregraft 50 System is only used on the back table in the operating room to rinse and filter an adipose tissue graft and prepare the graft for eventual injection back into the same patient during the same surgical procedure. The Puregraft 50 System is a bag with two tubing stubs/ports (tissue and drain) and is designed to harvest, rinse and filter the adipose tissue, and subsequently drain excess rinse solution away from the adipose tissue. The rinsed and filtered adipose tissue is then removed from the Puregraft bag using syringes (user supplied) and ultimately transplanted back into the same patient. The Puregraft 50 System includes a slider tool that is attached to the exterior of the Puregraft bag. The slider is used to compress the Puregraft bag as a means to facilitate the movement of liquids through the filter mesh and out of the Puregraft bag through the drain stub/port as waste.

6.6 Proposed Mechanism of Action of Cell Enriched Autologous Fat Grafts

The proposed mechanism of action of autologous fat grafts enriched with ADRCs prepared with both the Puregraft and Celution Systems is postulated to be follicular niche stimulation. This stimulation is believed to occur through modulation of inflammation, promotion of angiogenesis and prevention of cell apoptosis. Studies suggest that cell enriched autologous graft therapy changes the inflammatory response and augments the regenerative response. Studies have detected significant amounts of paracrine growth factors, which have been shown to facilitate vascularization, and as well as those associated with anti-inflammatory effects, thereby, ameliorating injury by proinflammatory cytokines. Viability characterization of ADRCs as described above in addition to pre-clinical animal data from Cytori and other published reports support this hypothesis.

7 STUDY TREATMENTS

Subjects will be randomized 2:2:2:1 to active treatment (autologous fat enriched with ADRCs), autologous fat alone control, or no-fat control as follows:

Active (0.5×10^6 ADRCs/cm^2 scalp):	20 Subjects
Active (1.0×10^6 ADRCs/cm^2 scalp):	20 Subjects
Autologous fat alone control:	20 Subjects
No-fat control (saline)	10 Subjects

The study treatment will be administered as subcutaneous injections of either fat or saline into the subcutaneous fat layer of the scalp (40cm^2 of scalp) of each subject. Each square centimeter of scalp will be injected with 0.1 mL of purified autologous fat or saline followed by separate injection of either low or high dose ADRC injection per cm^2 scalp, or saline (fat alone control and the no-fat control). To account for the variability seen in advanced grades of hair loss (Norwood Grade II and IV), treatment areas will be focused in the mid-scalp and crown (vertex).

The leading edge of hair loss will not be treated, including the peri-orbital region as fat grafting in the peri-orbital region has been associated with higher-risk complications.

7.1 Product Description – Cell-enriched autologous fat

The active treatment used for the STYLE Trial will be cell-enriched autologous fat obtained from the study subject's own adipose tissue which is prepared using the Puregraft and Celution Systems.

The excipients in the cell suspension are composed of residual Celution System reagents and diluent. Specifically, the residual reagents are collagenase (<0.005 Wünch Units/mL) and thermolysin neutral protease (< 30 caseinase Units/mL). The diluentis Lactated Ringers solution (USP).

Adipose tissue processing is detailed in both the *Puregraft* and *Celution System Users Manuals*. Preparation of the active study treatment is provided in *the Study Reference Manual*.

7.1.1 Active Treatment Dose Control

Autologous adipose purified with the Puregraft System can be readily removed directly with a sterile 1mL syringe to obtain a volume of 0.1mL for injection.

ADRC Cell count and viability will be controlled using the NucleoCounterAutomated Cell Counting System (Enfield, CT) at each site using the following acceptance criteria:

- Nominal cell count: 40 x 10^6 ADRCs
- A minimum cell count within 50% of the nominal cell count is required (i.e., a dose as low as 20 x 10^6 ADRCs is acceptable if 40 x 10^6 ADRCs is not be available)
- Cell viability: ≥ 70%

  If cell viability is <70%, as determined by the NucleoCounter Automated Cell Counting System, the subject will not be treated.
- Negative result in Gram stain testing (see *Section 7.3*)

7.2 Product Description – Control Doses

The fat alone control dose will be purified autologous tissue prepared by the Puregraft System that is not enriched with ADRCs but with saline. The amount of fat injected will be 0.1 mL/cm^2 of scalp. The fat alone control dose will also include injection of a saline solution which is mixed with 0.1mL to 0.2 mL of the study Subject's own freshly drawn blood to achieve a dilution that is visually indistinguishable from ADRCs. The saline injection of the fat-alone control must test negative in a Gram stain test of sterility prior to being administered (see *Section 7.3*). Preparation of the fat-alone control dose is provided in *the Study Reference Manual*.

The no-fat control dose will be 0.1ml/cm^2 of scalp of saline injected (delivered by a blunt tip cannula) followed by a second matching dose of saline solution (via a 25G needle) to 0.1ml/cm^2 of scalp.

7.2.1 Justification of Control Dose

To reduce the risk of bias (selection bias, performance bias, detection bias and attrition bias), all patients will undergo pre-specified screening procedures, fat harvest, and injection of active treatment or placebo. The justification and rationale of the placebo dose arm include:

1. In the presence of a concurrent placebo control group, demographics and patient selection is more likely to be balanced allowing for more reliable interpretation of study results.

2. Minimize the potential of the Hawthorne effect creating a positive impression of efficacy that may overstate the actual treatment effect.

7.3 Study Treatment Pre-Injection Sterility Testing

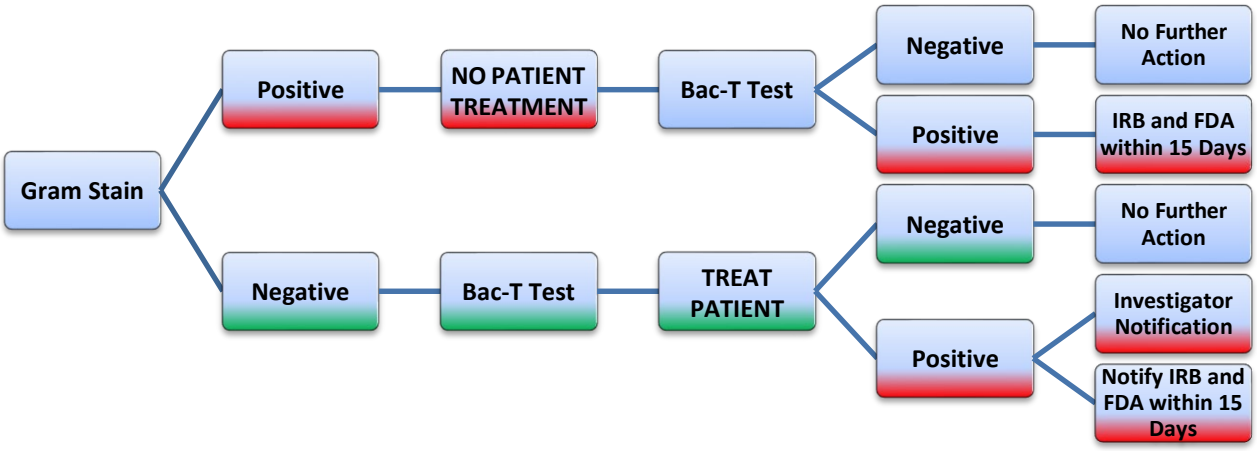
Following cell processing in the Celution System, sterility testing will be performed as described below and more fully in the *Study Reference Manual*.

A negative Gram stain test result is required prior to injection of ADRCs and/or fat alone control. A negative Gram stain test result is not required prior to injection of saline in the no-fat control arm. If the sample is determined to be positive for bacteria then the cellular administration procedure must be stopped and the subject should not receive any study treatment.

Further testing (BacT Alert Culture and Sensitivity) will be performed in order to test for the presence of any low level microbial contamination that might not be apparent in the gram stain test. Should a culture be deemed positive for microbial activity, the investigator will be immediately notified. The study patient will be evaluated and a course of treatment and/or antibiotics may be administered, as determined by the study investigator. The source of the contamination will be evaluated as appropriate. The FDA and IRB will be notified within 15 days of the investigator being made aware of any positive test results.

The following flow chart describes the activities associated with positive or negative outcomes in these two tests of sample sterility.

Figure 3: Sterility Testing of ADRC and Fat Alone Control Samples



7.3.1 ADRC Characterization

In order to characterize the phenotype of ADRCs obtained from patients with alopecia androgenetica, adipose tissue will be obtained during the elective cosmetic liposuction.; up to 360 mL of this tissue (maximum that can be processed by Celution Device) will be used to prepare the active study treatment (ADRCs) using the Celution System. Once it is determined that the cell dose has been achieved according to criteria described in *Section 7.1.1*, any remaining adipose tissue may be shipped to an outsourced facility of the Sponsor (if within two hours of the outsourced laboratory) according to procedures outlined in the *Study Reference Manual*.

In the Sponsor's outsourced contract laboratory, ADRCs will be prepared from collected adipose tissue using the same Celution System as used in the clinic and the cell output characterized using colony forming unit – fibroblast (CFU-F), a measure of the number of adipose stem cells, and multiparametric flow cytometry analyses used to define the major non-progenitor cell populations in ADRCs. In the flow analyses ADRCs will be stained using antibodies directed to CD31, CD34, CD136 and CD45 proteins. Based on the expression of these four markers, the major populations will be defined as follow:

Leukocytes	CD45+
Endothelial Cells	CD34+/CD31+/CD45-
Stromal Cells	CD34+/CD31-/CD45-
Mural cells	CD34-/CD31-/CD45-/CD146+

If sufficient cells are available, additional characterization of subpopulations will be performed using antibodies such as CD3, CD14, CD19, and CD16/56.

8 STUDY ASSESSMENTS

All assessments will be conducted at specific time points as outlined in this section and in the Schedule of Assessments in *Appendix A*.

8.1 Medical History, Physical Examination & Vital Signs

A complete medical history will be collected at the Screening Visit and will include demographic information as well as current and past medical conditions. Updated medical history information is to be collected at the Day -1 including any event that has occurred since the Screening Visit that could be considered an adverse event. Any adverse event that occurs after the ICF is signed and prior to administration of the study drug is to be recorded as an update to the Medical History.

Physical examinations should be based on the following body systems: general appearance, head (ear, eyes, nose and throat), cardiovascular, respiratory, abdomen, musculoskeletal, neurological, lymph nodes, and skin. Vital signs to be obtained include the following:

- Blood pressure (systolic and diastolic; mm/Hg)
- Heart rate (beats per minute)
- Body temperature (°F)
- Respiration rate (per minute)

8.2 Hair & Scalp Evaluation Assessments

The physical status and satisfaction of the subjects' scalp and hair will be evaluated using several assessment tools. The assessment tools are listed below and detailed information and instructions provided in the *Study Reference Manual*.

- Hair Investigator Satisfaction Survey
- Trichogram analysis
- Global photography

8.3 Prior and Concomitant Medications

Any medication a subject receives is considered a concomitant medication, and must be recorded in the subject's source documentation throughout the study. All concomitant medications will be recorded in the eCRF from 90 days prior to screening through 24 weeks post procedure.

Information to be recorded on the eCRF will include: generic medication name, route of administration, dosage, indication, start date, and stop date. Medications used as part of the liposuction and injection procedure do not need to be recorded in the eCRF but should be recorded as part of the operative records. As needed analgesic medications will be recorded by the subject's in a daily medication diary for the 14 days immediately preceding the next study visit.

8.3.1 Prohibited Medications

Subjects should not receive the following medications:

- Minoxidil, or any oral or topical medication including over the counter and herbal medications for the treatment of hair loss within 6 months of study screening, or finasteride or dutasteride within 12 months of study screening

- Treatment with an investigational product or procedure within 30 days of study screening

- Systemic steroids exceeding prednisone 10 mg daily (or equivalent)
- Biologic agentsor immunosuppressive medications within 90 days of the Screening Visit

If treatment with any prohibited medication becomes necessary during study participation, the subject will be discontinued from the trial.

8.4 Laboratory Procedures

All laboratory assessments will be performed locally at each center's laboratory by means of their established methods (using site specific laboratory normal values). Blood and urine samples should be taken using standard techniques and samples should be stored and shipped according to the laboratory guidelines.

8.5 Adverse Events

Adverse events will be recorded Starting on Day 1, immediately after study procedure has started and through to the End-of-Study (Week 24), Any adverse events experienced between signing the ICF and prior to administration of the study drug will be recorded in the medical history. See *Section 12* for more information pertaining to recording of adverse events.

9 STUDY VISIT REQUIREMENTS

The Schedule of Procedures is outlined in Appendix A.

9.1 Screening (within 28 days prior to procedure)

Subjects will undergo the following screening procedures:

- Written informed consent
- Inclusion and exclusion criteria evaluation
- Medical history
- Prior and concomitant medications
- Physical examination
- Laboratory Tests
    - CBC with Platelets
    - Electrolytes, alkaline phosphatase, bilirubin, AST, ALT, BUN, Creatinine
    - PTT, PT/INR
- Vital signs
- Pregnancy test (urine) for female patients of child-bearing potential
- Physician Hair Assessment questionnaire
- Evaluation of suitability for fat tissue harvest and liposuction procedure(see *Section 9.3.3.1*)

9.2 Pre-Operative Procedures (Day -1; performed within 24 hours of the liposuction)

- Confirm inclusion/exclusion criteria
- Physical Examination
- Vital Signs
- Assessment for Adverse Events
- Concomitant Medications
  - Collect daily medication diary completed for 14 days immediately preceding visit
- Laboratory Tests
  - CBC with Platelets
  - Electrolytes, alkaline phosphatase, bilirubin, AST, ALT, BUN, Creatinine
  - PTT, PT/INR
- Pregnancy test (urine) for female patients of child-bearing potential
- Investigator and Subject Hair Assessment questionnaire

The following tests are to be performed:

- Global Photography
- Trichogram with tattooing

9.3 Procedure Day (Day 1)

9.3.1 Fat Harvest

9.3.1.1 General requirements

- Fat harvest will be performed on the day of treatment as part of an independent, elective cosmetic liposuction.
- Fat harvest planning should include assessment of patients general health condition to undergo the procedure
- Standard tissue calipers or expert plastic surgical examination should be used to assess possible body sites for subcutaneous fat tissue. Patients should have greater than or equal to 2 cm of subcutaneous fat tissue available in each contemplated area to be suitable for liposuction
- Prepare up to 3 sites, including the preferred abdomen and flanks along with the inner and the outer thighs and the posterior and anterior thighs. To estimate harvestable fat from the harvest site the following guideline may be used: Estimated fat from the harvest site = volume of the site/8 = length of the marked skin x width of the marked skin x height (i.e. caliper skin-fold thickness) / 8. All patients who have inadequate fat deposits (i.e. < 200 ml of lipoaspirate from 3 bilateral sites) are to be excluded from the study. Any patient with an area of active skin infection in the site of lipoharvest will be excluded from the study.
- As noted elsewhere in this protocol, fat harvest should NOT be performed on patients who have received any anticoagulant within 1 hour of liposuction, substantial anticoagulation (e.g.: GIIb/IIIa inhibitor class drugs) within the two weeks prior to fat harvest, or who have an abnormal aPTT.
- Fat tissue should be obtained under sterile technique using local anesthesia with or without conscious sedation. General anesthesia should not be used.

9.3.1.2 Fat Harvest Procedure

Fat harvest from small volume liposuction is a standard procedure practiced by trained physicians in a variety of settings and using a variety of techniques. However, a specific set of guidelines have been established for the collection of fat that can then be used for the optimized preparation of ADRCs. These guidelines, which are recommendations and not requirements, include the following;

- Syringe-based fat harvest is preferred.
- Use up to 32 cm long, 3-5 mm inner diameter Toomey cannula with a standard tip
- 60 mL Toomey syringes are used for tissue acquisition
- Use 14 gauge, up to 30 cm, blunt LAMIS infiltrator for tumescent fluid administration
- Symmetric fat removal is required keeping the overall area of aspiration as small as possible
- The abdominal region is the preferred site for fat harvest

1. Local anesthesia with or without conscious sedation; general anesthesia is not permitted for fat harvest
2. Using sterile technique, prepare up to 3 sites, including the preferred abdomen and flanks along with the inner and the outer thighs and the posterior and anterior thighs.
3. Make an approximately 0.5 cm stab skin incision
4. Infiltrate tumescent solution using a blunt LAMIS infiltrator and a volume ratio of 1:1 of tumescent solution to fat to be harvested

Tumescent fluid formula:

- 500 mL of Lactated Ringers solution
- 20 mL of 1% Lidocaine
- 1 mg of epinephrine

5. To sufficiently induce vasoconstriction/hemostasis during the liposuction procedure a minimum of 500 mL of tumescent fluid must be used.
6. After approximately **10 minutes**, the adipose tissue is harvested through the same incision, using the aspiration cannula attached to the Toomey syringe
7. After the syringe is filled (complete filling is not required), cap syringe and replace with empty one
8. Continue fat harvest until desired volume is safely achieved, with the target volume of adipose tissue harvested limited to approximately 450 mL
9. Fat harvest will be limited to areas where tumescent fluid has been infiltrated
10. Vital signs are monitored continuously during liposuction procedure
11. Close surgical incision with appropriate suture
12. Apply pressure bandage immediately upon conclusion of tissue harvest

NOTE: Approximately 0.5 mL blood must be drawn and delivered to the unblinded staff prior to dose preparation. The blood will be used to prepare the fat alone control (see Section 7.2).

9.3.1.3 – Fat Harvest Stopping Rules

The physician performing the fat harvest procedure should continuously monitor the patient for signs of significant bleeding from the puncture site(s) and overall hemodynamic stability. The liposuction procedure should be terminated if any of the following occur:

1. Drop in systolic blood pressure < 90mm/Hg that is unresponsive to volume or pressor support
2. Profuse or uncontrollable bleeding from the puncture site(s)
3. Rapid expansion of subcutaneous space at the liposuction site(s) related to bleeding into the subcutaneous space
4. Hemoperitoneum or pnuemopertinoeum
5. Hemothorax or pneumothorax
6. Evidence of perforation of a vascular structure that requires ligature or surgical control
7. Evidence of perforation into abdominal cavity, peritoneum or gastrointestinal organ

Should any of the above occur, the fat harvest procedure should be terminated and the patient treated according to standard of care. DO NOT PROCEED WITH INJECTION. Complete the study specific SAE form and notify the sponsor within 24 hours.

9.3.2 Between Fat Harvest and ADRC Injection

Vital signs will be monitored continuously between the fat harvest and cell injection procedures.

9.3.3 Fat + ADRC Injection

The following procedure is recommended for subcutaneous injection into the scalp for the treatment of baldness due to alopecia androgenetica:

<u>Autologous Fat & Saline Injection</u>
This fat or saline injection procedure will occur after the completion of the liposuction. Aseptic technique should be maintained throughout the procedure. A treatment grid will be prepared in the area to be treated. The grid is a piece of silicone rubber that is placed on the scalp of the subject in the desired position and a surgical skin marker is used to mark each of the holes which are spaced every centimeter. The recipient site is anesthetized using a local ring block with 1% lidocaine with 1:100,000 epinephrine. Aliquots of 0.2mL should be injected in a circular ring fashion and the dosage should be adjusted according to the response of the patient and the site of administration. The lowest concentration and the smallest dose producing the required effect should be given. The maximum dose delivered should not exceed 7mg/kg. Sedation may be employed to minimize patient discomfort at the discretion of the investigator. Tissue from the Puregraft 50 is prepared in separate, sterile 1mL luer lock syringes, and an 11-blade scalpel can be used to make a stab incision (incision is made at a strategic insertion point to facilitate access to the area to be treated) to allow insertion of a 0.9mm-1.2mm diameter blunt-tip cannula. This

cannula is then inserted into the subcutaneous adipose tissue plane and the tip is fanned into each 1 square centimeter grid to deliver 0.1mL of tissue or saline (no-fat control).

ADRC & Saline Injection
After preparation of the ADRCs, either the low or high dose of ADRC or saline will be injected using a 25G needle directly through the skin into the layer of subcutaneous adipose using the identical grid markings made in the paragraph described above. Additional local anesthesia ± sedation may be applied as deemed necessary by the investigator.

A summary of the clinical workflow is described in Appendix C.

9.4 Immediately Post-Injection (Day 1)

- Vital Signs will be monitored for one hour following the injection procedure
- HGB/HCT blood level will be evaluated
- Assessment of injection and fat harvest site
- Overall physical assessment

9.5 Post-injection Follow-up visits (Week 1)

- Physical examination
- Vital Signs
- Assessment for Adverse Events

9.6 Post-injection Follow-up visits (Weeks 6, 12, 24, and 52)

- Physical examination
- Vital Signs
- Assessment for Adverse Events

The following tests are to be performed:

-
- Global photography
- Physician hair assessment questionnaire

A summary table of all follow up evaluations is outlined in Appendix B: Schedule of Procedures

9.7 Early Termination Evaluation

Subjects that discontinue early from the study, unless consent is withdrawn, shall have an Early Termination (ET) evaluation. This visit shall take place as soon as possible after it is determined that the Subject will be withdrawn from the study.

If the ET Visit occurs prior to the Week 24 visit the observations and procedures for the ET Visit are the same as those required at the Week 24.

The reason for early withdrawal must always be clearly documented in the Subject's source documentation. Contact with the Subject must be attempted to determine overall health status, and contact details must be documented in the Subject's source documentation. If lost to follow-up, details of three contact attempts must be documented in the Subject source documentation and every effort must be made to determine if the Subject has expired.

10 RISK/BENEFIT ANALYSIS

10.1 Risks

The use of adult regenerative cells from adipose tissue and other sources has shown improvement in muscular (cardiac) function after injection into ischemic areas of the heart. The PRECISE Clinical Trial has shown an acceptable safety profile and signs of benefits following intramyocardial administration of ADRCs processed by the Celution System. Every potential complication of ADRC injections are unknown at this time; however injection of cells from adipose tissue have been delivered with guided intramyocardial injections with no clinical significant sequelae. A clinical trial of 12 patients with hand dysfunction and pain from scleroderma followed for 6 months showed minor adverse events related to subcutaneous injection, typical liposuction adverse events, and no adverse events directly related to ADRCs.

10.1.1 Subcutaneous Delivery Risk Analysis

Risks involved with subcutaneous delivered adipose plus cells include:

- Hematoma or bleeding
- Infection
- Inflammation, rash, or papules at the injection site
- Nerve injury, pain, paresthesias or sensory disturbances
- Diminished function
- Shock loss

Direct intramuscular injections of Celase has been carried out in rodent models showing a margin of safety of greater than 10 for injection of Celase into the heart muscle. In addition, intra-ventricular applications of ADRCs into rat hearts during efficacy studies did not result in adverse events over 12 weeks of follow-up. Further, as noted above, 21 patients treated by direct injection into the muscle of the heart in the course of the PRECISE study exhibited no adverse events associated with ADRC injection In addition, a study of 12 patients with subcutaneous injection in the fingers of patients with scleroderma showed minor adverse events and no serious adverse events.

10.1.2 Subcutaneous Injection Risk Management

Investigators and all study personnel will be trained in the details of all aspects of the study procedures. To minimize risks and increase the chances of a favorable clinical outcome the following measures are required:

- Enrollment of Subjects who qualify per the inclusion/exclusion criteria in the protocol
- Strict adherence to the study protocol
- Use sterile technique throughout the procedure
- Use standard of care for the monitoring of and treatment of possible adverse events following injection procedure

10.1.3 Celution & Puregraft System Risk Analysis

The investigators and all study personnel will be trained in the details of all aspects of the study procedures relevant to their particular area of responsibility.

- Train investigators and all study personnel in the details of the operation of the Celution & Puregraft System.
- Inspect the package integrity and sterility indicators on all disposables used with the devices and maintain sterility of the fluid paths.
- Follow Instructions for Use for the Celution & Puregraft Systems, including all warnings, precautions and contraindications.

10.1.4 Overall Study Risk Management

The following measures implemented by Kerastem will minimize the risks associated with patients' participation in clinical studies:

- Kerastem selects personnel (Kerastem employees, agents, licensees, and clinical investigators at the sites) with extensive experience in conducting clinical studies and in performing procedures involved in the protocol including fat harvest and procedures involving the hands
- All examinations, treatment procedures, and interpretation of clinical data generated during the study is directed, overseen and analyzed by an appropriately licensed and credentialed physician who has been trained to the clinical study protocol.
- Kerastem developed the clinical protocol and training programs to ensure that the study personnel at Kerastem and at the clinical sites have a strong knowledge and understanding of the clinical protocol, including patient selection criteria and procedure requirements.
- Kerastem will ensure that the investigators are trained to the procedure requirements in the protocol, and the Instructions for Use for the Celution and Puregraft Systems.
- Kerastem carefully developed patient eligibility criteria for the investigation including clearly defined inclusion and exclusion criteria to ensure that only properly selected patients will be enrolled in the clinical study.
- The protocol is designed so that patient treatment and follow-up procedures will be consistent with those of the clinically established standard of care.

10.1.5 Fat Harvest Risk Analysis

The risks of standard small volume liposuction in healthy patients are known and are minimal and recovery is usually fast. Following standard liposuction the following effects can be expected:

Common

- Edema and redness of the liposuction areas for a few days
- Moderate contusion of the liposuction areas for a few months
- Uncommon
- Persistent edema

- Persistent bleeding
- Hematoma
- Visible puncture sites

Rare

- Infection
- Deep Vein thrombosis (DVT)
- Persistent bleeding requiring transfusion

10.1.6 Fat Harvest Risk Management

The Investigators and all study personnel will be trained in the details of all aspects of the study procedures. Standardization of fat harvest techniques is critical to a good clinical outcome. To minimize risks and increase the chances of a favorable clinical outcome the following measures are required for the liposuction procedure:

- Performed by an appropriately licensed and credentialed physician
- Monitoring of vital signs throughout the procedure.
- Sterile technique is followed throughout.
- The adipose tissue is handled gently at all times.
- HGB, HCT prior to and 1-2 hours post-procedure
- To sufficiently induce local vasoconstriction/hemostasis during the fat harvest procedure, a minimum of 500 mL of tumescent fluid is used containing:
    - 500 mL of Lactated Ringers solution
    - 20 mL of 1% Lidocaine
    - 1 mg of epinephrine
- A blunt 14 to 16 gauge LAMIS infiltrator (or equivalent) will be used for infiltration with tumescent solution
- After ~10 minutes, the adipose tissue may be harvested through the same incision, using the aspiration cannula attached to a syringe
- A blunt cannula with a minimum inner diameter of 3 mm is preferred for lipoaspiration.
- Lipoaspiration is recommended to be done manually using a syringe (60 mL Toomey syringe is preferred).
- Enrollment of only patients who qualify per the inclusion / exclusion criteria defined in the protocol) including screening blood work
- Strict adherence to the study protocol
- Standard of care for the monitoring of and treatment who experience any adverse event for liposuction
- Target volume of adipose tissue is limited to approximately 450 mL
- Close surgical incision with appropriate suture
- Apply pressure bandage immediately upon conclusion of tissue harvest

Fat harvest should <u>NOT</u> be performed on patients who have received any anticoagulant within 1 hour of the procedure, substantial anticoagulation (e.g.: GIIb/IIIa inhibitor class drugs) within two weeks prior to fat harvest, or who have an abnormal PTT.

10.2 Potential Benefits

This clinical investigation is designed as a safety and efficacy study. Therefore, it is not known at this time whether any direct subject benefit can be expected. Given the proposed mechanism of action of autologous adipose enriched with or without ADRCs, we expect there may also be a beneficial effect in the treatment of baldness due to alopecia androgenetica. Previous ex-US patient experience with similar inclusion/exclusion criteria documented encouraging positive efficacy results and a favorable benefit to risk profile (abstract accepted at 2014 International Federation of Adipose Therapeutics and Science (IFATS) Annual Meeting-November 2014).

11 STATISTICAL METHODS AND DATA ANALYSIS

This is a multi-centre, single-blinded, randomized, parallel group, controlled study to evaluate the preliminary safety of cell-enriched autologous fat compared to placebo in patients with baldness due to alopecia androgenetica. The primary endpoint will be the safety and tolerability of the procedure.

An analysis of covariance (ANCOVA), with the baseline measure used as a covariate, will be used for the analyses of the secondary efficacy endpoints. Comparisons of each active arm with placebo will be made using Dunnett comparisons. The ITT population will be used for the primary analysis; the analysis will also be performed in the PTE population and will be considered as supportive of the ITT analysis.

11.1 General Considerations

All statistical tests will be two sided, and statistical significance will be assessed with respect to a nominal p-value of 0.05. Before the first data review meeting of the DMC is held, a separate statistical analysis plan (SAP) will be completed, providing detailed methods for the analyses outlined in the following subsections. The SAP will detail all planned analyses and will serve as a statistical programming requirements document.

11.2 Determination of Sample Size

The sample size for the trial has been set at 70, based on clinical considerations and is not based on formal power calculations.

The objective of the STYLE Trial is to assess the safety and preliminary efficacy of cell-enriched autologous adipose delivered via a subcutaneous route in the treatment of baldness due to alopecia androgenetica. As the primary endpoint is safety and tolerability, the investigators believe that a sample of 20 subjects per arm and a 10 patient no-fat saline control is adequate.

11.3 Data Analyses

Safety and efficacy endpoints will be summarized by treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum), for quantitative variables and frequencies and percentages for categorical variables. Laboratory data will also be summarized using shift tables

between before procedure and at Day 1, post procedure, with values categorized as less than lower limit of normal range, within normal range, and above upper limit of normal range.

For quantitative efficacy variables, summaries will be provided at each post-baseline visit time point. Additionally variables will be analyzed using ANCOVA models with adjustment for the baseline value of the variable.

Related adverse events will be analyzed separately for those related to ADRCs and the delivery of ADRCs (i.e., injection site such as shock loss). A separate safety analysis will be performed for Adverse Events of Interest (Appendix B, Adverse Event Terminology and Grading).

11.3.1 Primary Endpoint Analysis

The primary endpoint for the study is safety and tolerability through 24 weeks

The hypotheses are:

> Adverse event rates through 24 weeks for active treatment will be less than or equal to adverse events rates published for autologous fat grafting.
>
> Vital sign abnormalities through 24 weeks for active treatment will be less than or equal to those published for autologous fat grafting.
>
> Physical exam abnormalities through 24 weeks for active treatment will be less than or equal to those published for autologous fat grafting.

The corresponding null hypotheses are that the adverse event rates will be greater for active treatment arms than for placebo.

Statistical testing will not be performed for these hypotheses, but the safety endpoints will be evaluated clinically.

11.3.2 Secondary and Exploratory Endpoint Analysis

The secondary endpoints are change from baseline in the (a) Average Trichogram growth rates at 24 weeks, (b) Average Trichogram density rate at 24 weeks, and (c) global photographs at 24 weeks and (d) hair Investigator Satisfaction Survey at 24 weeks. Multiplicity adjustment will not be made when testing the three secondary endpoints.

Exploratory endpoints are listed in Section 4.5. As these are exploratory, p-values for each analysis will not be corrected for multiple comparisons. These analyses will provide evidence concerning the safety of effectiveness of the product.

11.3.3 Subgroup Analysis

Statistical analysis of efficacy and safety endpoints will be performed in the total group.

11.4 Background, Demographic Analyses

Demographic data, medical history, concomitant disease will be summarized by means of descriptive statistics (n, mean, SD, median, minimum and maximum) or frequency tables, stratified by treatment.

11.5 Subject Disposition & Analysis Populations

Reasons for withdrawal post-randomization will be summarized.

The treatment analyses will be performed on intent-to-treat basis as well as on a per-treatment-evaluable basis, as defined below:

Safety: All treated subjects; subjects will be analyzed as treated.

Intent-to-Treat (ITT): All randomized subjects; randomization will occur on procedure day prior to liposuction. Subjects will be included in the analysis as randomized

Per-Treatment-Evaluable (PTE): All randomized subjects who have received treatment and follow-up information is available. Protocol violators, where the violation is judged to affect the interpretation of the treatment effect will be excluded. All exclusions will be made prior to the breaking of the treatment blind.

11.6 Handling of Missing Data

Safety data will not be imputed.

PTE data will not be imputed.

Missing efficacy data will be imputed for the ITT analysis population. For missing data caused by worsening of scleroderma (either hand or systemic manifestation), the missing value will be replaced by the least favorable observation from the prior Visits excluding baseline. For other missing data, last observation carried forward will be the primary method of imputation. As a sensitivity analysis, multiple impute ion methods (SAS PROC MI and PROC MIANALIZE) will be used.

For the analysis of quality of life, missing responses to individual questionnaire items will be imputed using the methods prescribed by the questionnaire vendor.

11.7 Protocol Deviations

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as “minor” or “major” in cooperation with the Sponsor. Deviations will be defined prior to un-blinding. Major deviations may result in removal from the PTE analysis population.

11.8 Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will be comprised of medical specialists and a biostatistician who are not participants in the study. The DMC will be provided with all safety data as well as efficacy data for the primary and secondary endpoints in order to fully

evaluate the benefit to risk profile of the study procedures. The DMC will be responsible for the review of the data and generate recommendations on the conduct of the trial.

The DMC will be asked to review data and generate recommendations after 10, 20 and 40 subjects have at least 1 week of follow-up.

11.8.1 Adverse Events Initiating Safety Review

The Sponsor is to be informed of the following adverse events within 24 hours of the site becoming aware of the event:

- Gangrene of the scalp in two (2) or more within fourteen (14) days of the procedure
- Infection of the scalp requiring hospitalization and intravenous antibiotics in two (2) or more patients within seven (7) days of the procedure

Within 24 hours of notification, the Sponsor will report the event to the DMC Chair for evaluation. The DMC Chair will review the event and decide whether to convene a meeting of the DMC.

In all cases, the DMC Chair or the DMC will be responsible for recommendations to continue the trial, continue the trial with modifications, pause the trial such that further evaluation can be conducted, or terminate the trial.

12 ADVERSE EVENTS / SERIOUS ADVERSE EVENTS

12.1 Definitions

An **adverse event (AE)** is defined as any undesirable experience occurring to a Subject during the course of the study, whether or not it is related to the test material or the study procedure. Expected adverse events are those that are listed as known risks of the liposuction or injection procedure including those described in this protocol, informed consent, and/or the Investigator's Brochure.

A **serious adverse event (SAE)** is defined as any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
- Requires or prolongs Subject hospitalization
- Results in persistent or significant disability or incapacity
- Is an important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the Subject or require intervention to prevent one of the above outcomes
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate.

An **Unanticipated Adverse Device Effect** is defined as any serious adverse effect on the health and safety or any life-threatening problem or death caused by, or associated with the Celution or Puregraft system devices, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application or any other unanticipated serious problem with the Celution or Puregraft system devices that relates to the rights, safety or welfare of subjects.

12.2 Procedures for AE Reporting

All AEs will be recorded by the investigator or designee on the appropriate electronic case report form (eCRF). Events that occur prior to the liposuction-related activities, including those that are considered serious, are to be recorded in the medical history. Events, including SAEs, which occur after liposuction-related activities are initiated on procedure day, are to be recorded on the AE eCRF. The investigator will evaluate the relationship of the adverse event to both the test material and study procedure as unrelated, unlikely, possibly, probably, or definitely related and will record the findings, including all pertinent details of the event on the eCRF.

In addition, the Investigator or designee will report any serious adverse events, including UADE, occurring during this study to the Sponsor and Medical Monitor as soon as possible, but no later than 24 hours after the Investigator first identifies the adverse event.

The Investigator will take appropriate measures to ensure the subject's well-being and document these measures on the appropriate eCRF.

All serious adverse events experienced will be monitored until the event has resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Medical Monitor, or until there is a satisfactory explanation for the changes observed.

12.3 Adverse Event Terminology

Specific adverse events of interest are described in *Appendix B, Adverse Event Terminology and Grading* (from National Cancer Institute Common Terminology Criteria for Adverse Events). When an AE of interest occurs, the Investigator will apply the terminology in Appendix B, *Adverse Event Terminology and Grading* and indicate the grading.

12.3.1 Injection Site Related Adverse Events

Injection site related adverse events are outlined in Appendix B, *Adverse Event Terminology and Grading* (i.e. from National Cancer Institute Common Terminology Criteria for Adverse Events).

13 EMERGENCY DEVIATION FROM THE PROTOCOL

In case of an emergency threatening the continued well being of the Subject, the Investigator may deviate from the protocol. The circumstances necessitating the deviation and the

intervention(s) required will be recorded on the eCRF. The Sponsor must be notified as soon as possible, but no later than 5working days after event(s) occurred.

14 REGULATORY OBLIGATIONS AND STUDY REQUIREMENTS

14.1 FDA and Institutional Review Board Approval

Study initiation will not take place until the following regulatory requirements are met:

- Food and Drug Administration (FDA) approval with accompanying approval letter.
- Local Institutional Review Board (IRB) full approval with accompanying approval letter.

14.2 Informed Consent

Written informed consent will be obtained from all Subjects prior to the initiation of any study specific procedures. No tests or procedures required in this protocol that are outside the standard practice for treating hamstring tears will be initiated prior to obtaining written informed consent. The original ICF will be filed in the Investigator Site File.

14.3 Monitoring Procedures and Data Management

14.3.1 Site Qualification

A site qualification visit will be performed to evaluate site facilities, Investigator qualifications, adequacy of staffing, and understanding of clinical and regulatory requirements.

14.3.2 Site Training

All Investigators and appropriate study staff will be required to participate in a site training (or initiation if appropriate) to provide orientation and training to the Celution System, the Puregraft System, the STYLE Trial protocol, eCRFs and other study related documents and procedures.

14.3.3 Monitoring

During the course of the study, a representative of the Sponsor will make site visits to review protocol compliance, compare eCRFs and individual subject's medical records, assess test article accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that Subject confidentiality is maintained.

Reviewing the eCRFs for completeness and clarity, and cross-checking with source documents and reviewing any discrepancies or issues with the Investigator will be required to monitor the progress of the study. Moreover, regulatory authorities (United States Food and Drug Administration) and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be

required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality.

14.3.4 Reporting Requirements

The following reports are required of the Investigator:

- eCRFs for each subject entered into the study (this includes all screen failures as well)
- Reports of any SAEs within 24 hours of becoming aware of events
- Final report at the conclusion of the study
- Progress reports to the Sponsor, clinical monitor, and IRB at regular intervals – at least yearly
- Report to the Sponsor, within 5 working days, of withdrawal of approval by the reviewing IRB
- Report to the Sponsor and IRB of any emergency changes made to the protocol to protect the life or physical wellbeing of a Subject no later than 5working days after the emergency occurred

14.3.5 Data Management

Data management will be conducted by the Sponsor or designee, and will include a data management plan and data verification guide developed according to protocol requirements.

14.4 Study Center and Investigator Requirements

To protect the rights and welfare of Subjects, the study will be conducted in conformance with the Declaration of Helsinki, the guidelines on GCPs, Code of Federal Regulations (21 CFR 11, 50, 56, 812, 814 and 820) and applicable local laws and regulations pertaining to the conduct of the study and the protection to human Subjects.

All Investigators, sub-investigators and study personnel are required to read and follow the protocol, as well as any literature that accompanies the products prior to conducting the study procedure for the first time. In addition, all Investigators will sign and date the Investigator Statement Page of this protocol. All Investigators participating in this study will be trained in the proper use of the study procedure and in the components of this protocol.

The Principal Investigator (PI) is ultimately responsible for the conduct of this study; however, he/she may designate a member of his/her staff to assist with the collection of data and completion of eCRFs. The designee(s) will be documented on an authorization form that is signed by the PI and kept in the Regulatory Binder, to be updated as necessary. Current copies of the authorization form will be forwarded to the Sponsor.

Obtaining informed consent in accordance with national policy is mandatory for Subject participation. All Subject data is kept confidential and procedures will be implemented to ensure that Subject confidentiality is not compromised.

If additional materials are used for screening and recruitment or provided to study Subjects (i.e. advertisements, recruitment materials) they must be approved by Kerastem and the Institutional Review Board at the clinical site prior to use. Documentation of the approved informed consent must be provided to Kerastem prior to study commencement at the clinical site.

After a Subject has signed the Informed Consent Form, an eCRF will be initiated. After this point, the reason(s) must be documented on the report form for any Subject who has dropped, withdraws, or for any reason cannot complete this study.

14.4.1 Study Center Requirements

Due to the nature of the STYLE Trial, centers will be considered for participation only if the meet the following minimum facility requirements:

1. Familiarity with FDA authorized IDE and/or IND Clinical Trials within the United States
2. Affiliated pharmacy or laboratory capable of performing clinical trial randomization and cell dose preparation
3. Ability to adhere to strict compliance with the STYLE clinical protocol for all study related procedure and observations.
4.

15 PUBLICATIONS

Following completion of the study, Kerastem will present the study data in a clinical study report that will be delivered to the FDA according to US regulations.

In the event the investigator wishes to present or publish any study data (partial or complete), he/she must submit the presentation / publication draft to Kerastem for review within 30 days of the planned submission or presentation.

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APPENDIX A: SCHEDULE OF PROCEDURES

	Pre-procedure Assessment	Procedure Day		Post-Operative Follow-up Week				
	Day -28 to Day-3	**Day -1**	**Day1**	**1 ± 1 day**	**6 ± 3 days**	**12 ± 1 wk**	**24 ± 2 wks**	**52 ± 2 wks**
Informed consent	X							
Confirm Inclusion / Exclusion criteria	X	X						
Medical history including Demographics	X	X[1]						
Physical examination	X	X	X	X	X	X	X	X
Vital signs	X	X	X[2]	X	X	X	X	X
Laboratory tests	X	X	X					
Pregnancy test[3]	X	X	X					
Injection assessment	X							
Global Photography	X	X			X	X	X	X
Trichogram capture		X			X	X	X	X
Investigator Hair Satisfaction Questionnaire	X	X			X	X	X	X
Subject Hair Satisfaction Questionnaire		X			X	X	X	X
Randomization			X					
Sterility Testing			X					
Injection Procedure			X					
Adverse Events			X	X	X	X	X	X

1. Adverse Events that occur prior to the liposuction-related activities, including those that are considered serious, are to be recorded in the medical history.
2. Vital signs will be monitored according to institutional procedures; it is suggested that vitals be monitored frequently during the fat harvest, between fat harvest and cell injection and during cell injection procedure and for at least one hour following the injection procedure
3. Women of child-bearing potential

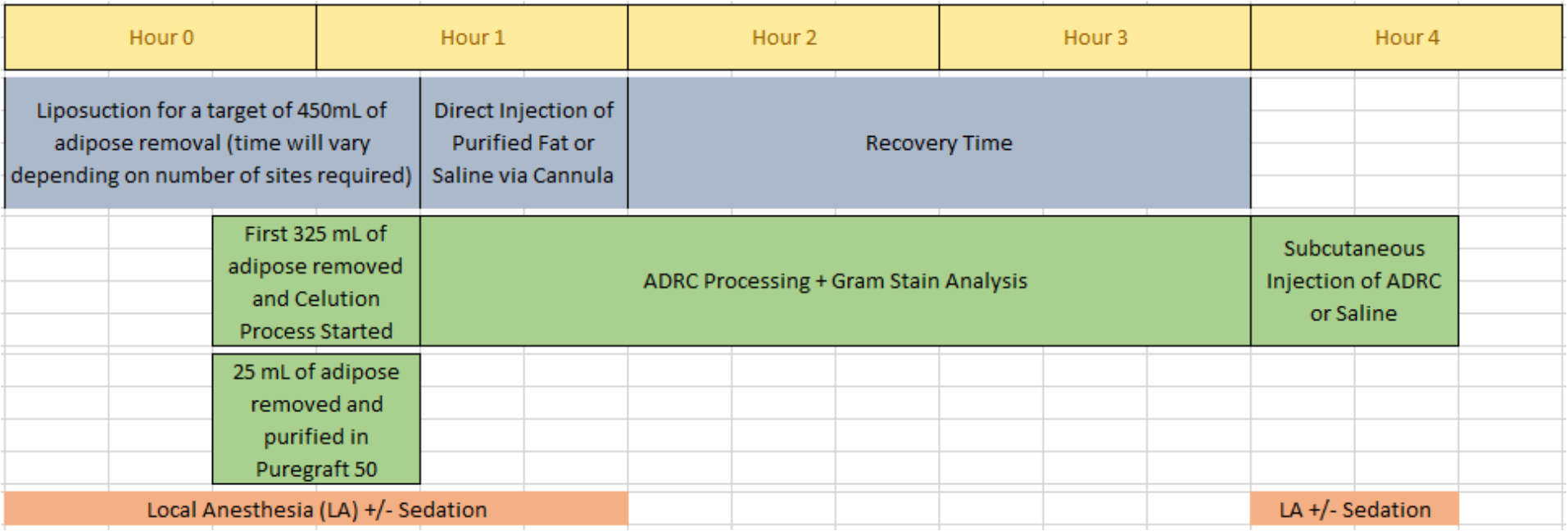
APPENDIX B: ADVERSE EVENT TERMINOLOGY AND GRADING

(Adapted from National Cancer Institute Common Terminology Criteria for Adverse Events)

		Severity Grading				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Bruising	Localized or in a dependent area	Generalized	-	-	-
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	-	-	-
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	-	-	-
Injection site reaction/ extravasation changes	Injection site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	-	-
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
Hemorrhage/bleeding associated with surgery, intra-operative or postoperative	Hemorrhage with surgery	-	-	Requiring transfusion of 2 units non-autologous pRBCs beyond protocol specification; postoperative interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death

		Severity Grading				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Infection with normal ANC or Grade 1 or 2 Neutrophils at the site of liposuction or cell-enriched injection	Infection with normal ANC at the site of liposuction or ADRC injection	-	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
Pain at the site of liposuction or cell-enriched injection	Pain	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	-

APPENDIX C: SUMMARY OF CLINICAL WORKFLOW



Subcutaneous Transplantation of Autologous Cell Enriched Adipose Tissue For Follicular Niche Stimulation in EarlY Stage ALopEcia Androgenetica (STYLE): a Randomized, Blinded, Controlled Trial

STYLE Clinical Trial

Version B

24November2015

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STYLE TRIAL PROTOCOL APPROVAL FORM

Study Title:	Subcutaneous Transplantation of Autologous Cell Enriched Adipose Tissue For Follicular Niche Stimulation in EarlY Stage ALopEcia Androgenetica (STYLE): a Randomized, Blinded, Controlled Trial
Short Title:	STYLE Trial
Protocol Version A Date:	21 August 2015

This study protocol was subjected to critical review. The information it contains is consistent with the sponsor's current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, as amended in 2013, Good Clinical Practice (GCP) Consolidated Guidance in guidelines of the International Conference on Harmonization (ICH) E2 & E6, and 21CFR 11, 50, 54, 56, 812, 814 and 820. The study will also be carried out in keeping with all applicable laws, rules, and regulations.

Eric Daniels Chief Medical Officer Kerastem Technologies, LLC	Date (dd/mmm/yyyy)

INVESTIGATOR STATEMENT PAGE

Study Sponsor: **Kerastem Technologies, LLC**
Clinical Trial: **STYLE Trial**
Protocol Version A: 21August2015

Study Title: Subcutaneous Transplantation of Autologous Cell Enriched Adipose Tissue For Follicular Niche Stimulation in EarlY Stage ALopEcia Androgenetica (STYLE): a Randomized, Blinded, Controlled Trial

The information contained in this document and all information provided to you related to this protocol are the confidential and proprietary information of Kerastem (Sponsor) and except as may be required by federal, state or local laws or regulations, may not be disclosed to others without prior written permission of Sponsor. The Principal Investigator at each site may, however, disclose such information to supervised individuals working on the protocol, provided such individuals agree to be bound to maintain the confidentiality of such protocol information.

I agree to abide by the statement of confidentiality.

I agree to provide my curriculum vitae.

I agree to disclose if I was involved in an investigation or other research that was terminated, and an explanation of the circumstances that led to termination

I agree to conduct the study according to this protocol. Any changes in procedure will only be made if necessary to protect the safety, rights, or welfare of patients.

I agree to comply with the current ICH, GCP and CFR Guidelines.

I agree to conduct the study in person or to supervise the study.

I agree to ensure that all who assist me in the conduct of the study have access to the study protocol and any amendments and are aware of their obligations.

As an investigator for the STYLE Trial, I intend to commit to conducting the investigation in accordance with the investigator agreement, the investigational plan, Part 812 and other applicable FDA regulations and conditions of approval imposed by the reviewing IRB and FDA. I agree to supervise all testing of the device involving human subjects and will ensure that the requirements for obtaining informed consent are met. As an investigator, I am committed to provide sufficient and accurate financial disclosure information and update information if any

relevant changes occur during the investigation and for one year following the completion of the study.

Principal Investigator (Print Name and Title)

Principal Investigator (Signature) Date (dd/mmm/yyyy)

STUDY CONTACTS

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STYLE TRIAL - PROTOCOL SUMMARY

Title	Subcutaneous Transplantation of Autologous Cell Enriched Adipose Tissue For Follicular Niche Stimulation in EarlY Stage ALopEcia Androgenetica (STYLE): a Randomized, Blinded, Controlled Trial
Test Products	Celution® System (Celution Device, Celution Consumable Set and Celase) used for processing of Autologous Adipose Derived Regenerative Cells (ADRCs) combined with adipose tissue processed and purified with Puregraft® 50 System
Objective	The primary objective of this study is to evaluate the safety and feasibility of the Celution and Puregraft Systems in the processing and preparation of an autologous fat graft enriched with adipose-derived regenerative cells (ADRCs) in the treatment of early alopecia androgenetica.
Design	Prospective, Randomized, Controlled Safety and Feasibility Trial
Sample Size	70 patients (40 ADRC + adipose, 20 fat only control, 10 no-fat control)
Study Location	Up to (8) sites in the United States
Indication	Androgenic Alopecia (Androgenetica Alopecia, AGA)
Visit Schedule	Screening (Day -28 to Day -7), Pre-Procedure Day (Day -1)Procedure Day (Day 1), and follow up visits at weeks 1, 6, 12, 24 and 52 weeks
Treatment Arms	Subjects will be randomized 2:2:2:1 to receive either 0.1ml/cm^2 scalp of autologous fat enriched with 0.5 x 10^6 ADRC/cm^2 scalp (n=20), 0.1 ml/cm^2 scalp of autologous fat enriched with 1.0 x 10^6 ADRCs/cm^2 scalp (n = 20), 0.1ml/cm^2 scalp of autologous fat enriched with a matching saline control (fat alone control; n=20), or 0.1 ml/cm^2 scalp of saline enriched with a matching dose of saline (no-fat control; n=10). In each subject, 40 square centimeters of scalp will be treated. The study treatment will be delivered in the subcutaneous adipose layer of the scalp in via two separate injections – one of either 0.1ml/cm^2 scalp of adipose or saline followed by a second injection of ADRCs or saline per square centimeter of scalp.
Primary Endpoint	Safety & tolerability through 24 weeks
Secondary Endpoints	• Trichograms (Hair Growth) at 24 weeks • Trichograms (Hair Density) at 24 weeks • Global photographs to assess scalp coverage at 24 weeks

	• Hair Investigator Satisfaction Survey at 24 weeks
Exploratory Endpoints	• Trichograms (Hair Growth)at times other than 24 weeks • Trichograms (Hair Density) at times other than 24 weeks. • Trichograms (Hair Thickness) at times other than 24 weeks • Global photographs to assess scalp coverage other than 24 weeks • Hair Investigator Satisfaction Survey at times other than 24 weeks.
Safety Endpoints	Adverse events, Serious Adverse Events, UADEs
Inclusion & Exclusion Criteria	**Inclusion Criteria** 1. Males with a diagnosis of Alopecia Androgenetica 2. Females with a diagnosis of Alopecia Androgenetica 3. Males with hair loss consistent with Grades III, IIIA, III-Vertex, IV, IV-A, based on Norwood-Hamilton Scale (Figure 1) 4. Females with hair loss consistent with Grades I-3, I-4, II-1, II-2 based on the Savin Scale (Figure 2) 5. Provide written informed consent and comply with the study requirements 6. For women of childbearing potential: Negative pregnancy test at screening visit plus subject agrees to maintain two forms of contraception for the duration of the study. 7. Subject is willing to maintain a consistent hair length and natural hair color, without the use of any coloring agents, during the study period. 8. Ability to complete study procedures, patient surveys, and pictures. 9. Subject is ≥ 18 years of age. 10. Body Mass Index < 40kg/m^2 **Exclusion Criteria** 1. Subjects who have used minoxidil, or any oral or topical medication including over the counter and herbal medications for the treatment of hair loss within 6 months of study screening, or finasteride or dutasteride within 12 months of study screening 2. Treatment with an investigational product or procedure within 30 days or plans to participate in another clinical study 3. Subject who has previously failed or has been deemed non-responsive to a previous experimental hair loss treatment. 4. Subject must have no previous hair transplant, cell treatment, micro needling, or any other treatment in the last 6 months in the scalp. 5. Subject is currently suffering from an active autoimmune disease such as serum lupus erythematosus, or alopecia areata. Subject is currently suffering from dermatologic condition in the treatment area or has a significant scar in the hair treatment area that, in the opinion of the investigator, will make hair growth difficult (such as systemic burns,

	etc.). 6. History of autoimmune disease or organ transplantation or a patient on immunosuppressive medication(s). 7. Diagnosis of cancer, receiving active treatment 8. Active systemic infection 9. Requires chronic antibiotics, systemic corticosteroids 10. Use of systemic agents that increase bleeding or clotting, or disorders associated with these effects, including patients receiving GIIB/IIIa inhibitors within 2 weeks prior to the study procedure through to 1 week after the study procedure. 11. Clinically significant medical or psychiatric illness currently or within 30 days of study screening as determined by the investigator 12. Prior surgery in the treatment area 13. Any disease or condition (medical or surgical) that, in the opinion of the investigator, might compromise dermatologic, hematologic, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, or central nervous system function; or any condition that would place the subject at increased risk 14. Pregnant or lactating women or women trying to become pregnant 15. Known allergic reaction to components of study treatment and/or study injection procedure 16. Subject has any disorder that may prevent compliance to study procedures and visits 17. Subject who is part of the study staff, a family member or friend 18. Diabetes or thyroid disorder 19. Subject who has a sensitive, irritated, or abraded scalp area. 20. Women who have an alternate diagnosis that is associated with hair loss. 21. Body Mass Index < 18kg/m^2 22. Clinically significant abnormal findings on laboratory screening panels, including hemoglobin ≤ 10 g/dL. 23. Hepatic dysfunction, as defined as aspartate aminotransferase (AST), alanine aminotransferase (ALT), or bilirubin levels > 1.5 times the upper limit of normal range (x ULN) prior to randomization. 24. Chronic renal insufficiency as defined as a serum creatinine > 1.5 mg/dL in men or > 1.2 mg/dL in women. 25. An elevated PT/PTT, INR, or platelet count < 100 x 10^9/L

ABBREVIATIONS

ADL	Activities of Daily Living
AGA	Androgenic Alopecia
ADRC	Adipose-Derived Regenerative Cells
AE	Adverse Event
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
AFT	Autologous Fat Transfer
CFU-F	Colony Forming Units Fibroblast
CFR	Code of Federal Regulations
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ET	Early Termination
FPHL	Female Pattern Hair Loss
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ID	Identification
IFU	Instructions for Use
IV	Intravenous
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MPHL	Male Pattern Hair Loss
PI	Principal Investigator
pRBC	Pack Red Blood Cells
PTE	Per Treatment Evaluation
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
WBC	White Blood Cell

1 OBJECTIVE

The primary objective of this study is to evaluate the safety and efficacy of the Cytori Celution and Puregraft Systems in the processing and preparation of an autologous fat graft enriched with adipose-derived regenerative cells (ADRCs) in the treatment of early alopecia androgenetica.

2 BACKGROUND

2.1 Alopecia Androgenetica

Alopecia Androgenetica (AGA) is the most common form of both male pattern hair loss (MPHL) and female pattern hair loss (FPHL)[1,2] with the condition affecting approximately 50% of the male population and less than 45% of women going through life with a full head of hair. The degree of hair loss in the male patient is generally classified using the Norwood Hamilton Classification (Figure 1) and FPHL is evaluated based on the Savin scale (Figure 2)[1,3]. The incidence and prevalence of the condition are generally well documented in both genders. Stough and co-workers reported that in White males, 30% have AGA by age 30 and 50% by age 50 with lower incidences seen in African American, Chinese, and Japanese populations[3]. In a population based report looking at MPHL, the authors reported that in the 30-35 years age group, grade I hair loss was 51%, while grade II was 43% and grade VI was only approximately 19%--clearly highlighting early hair loss in the younger population[4]. Of the 1,005 men in the study aging from 30-50 years, 44% were found to have grades I-III hair loss.

In women, diffuse thinning and loss of hair density with maintenance of the frontal hairline describe the typical pattern of loss5. In one report, the prevalence of early, clinically detectable FPHL was 12% of females between 20-29 years of age and 25% by 49 years of age[2]. In the table presented below (Table 1), Gan and Sinclair documented the distribution of hair loss in 752 women using a modified 5-point grading scale[6]. Below the age of 40 years, 99% of women reporting loss documented early stage loss.

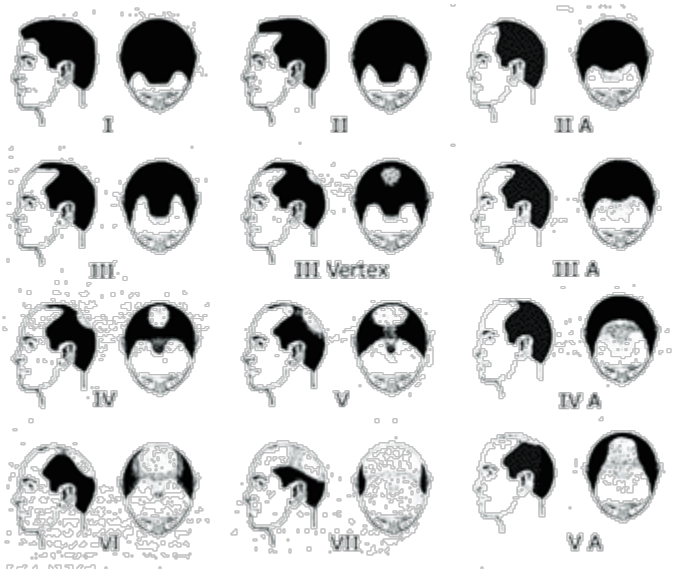
TableIV. Hair patterns in female subjects

	Hair thickness						
Age	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Total	1–stage 1
5–9	72 (100%)						–
20–29	50 (88%)	5 (9%)	1 (2%)	1 (2%)		57	7 (12.3%)
30–39	73 (83%)	14 (16%)		1 (1%)		88	15 (17.0%)
40–49	91 (75%)	28 (23%)		3 (2%)		122	31 (25.4%)
50–59	106 (72%)	29 (20%)	11 (7%)	1 (1%)		147	41 (27.9%)
60–69	73 (59%)	37 (30%)	11 (9%)	2 (2%)	1 (1%)	124	51 (41.1%)
70–79	58 (46%)	35 (28%)	24 (19%)	6 (5%)	2 (2%)	125	67 (53.6%)
≥ 80	23 (43%)	15 (28%)	8 (15%)	8 (15%)		54	35 (57.4%)
Total	474 (66%)	163 (23%)	55 (8%)	22 (3%)	3 (0.4%)	717	247 (32.2%[a])

[a]Adjusted to age.

In sum, a significant percentage of both male and female population suffer from AG at a relatively early age.

Figure 1—MPHL Norwood Hamilton Classification



Class I represents an adolescent or juvenile hairline and it not actually balding. The adolescent hairline generally rests on the upper brow crease.

Class II indicates a progression to the adult or mature hairline which sits a finger breath (1.5cm) above the upper brow crease, with some temporal recession. This also does not represent balding.

Class III is the earliest stage of male hair loss. It is characterized by a deepening temporal recession.

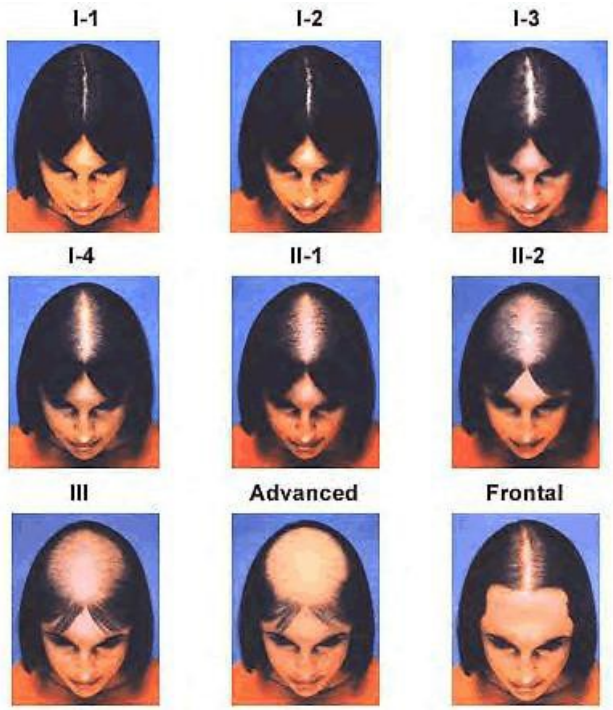
Class III Vertex represents early hair loss in the crown (vertex).

Class IV Is characterized by further frontal hair loss and enlargement of vertex, but there is still a solid band of hair across top separating front and vertex.

Class V the bald areas in the front and crown continue to enlarge and the bridge of hair separating the two areas begins to break down.

Class VI occurs when the connecting bridge of hair disappears leaving a single large bald area on the front and top of the scalp. The hair on the sides of the scalp remains relatively high.

Figure 2—FPHL Ludwig Scale



The current treatment regimen for alopecia androgenetica is a spectrum ranging from non-invasive medicinal approaches to robot-assisted surgical transplantation of thousands of follicular units. On the non-invasive side, the two medicines currently approved for treatment of genetic pattern alopecia by the FDA are finasteride (for men only) and minoxidil[8,9]. Both of these medicines carry untoward side-effects. For finasteride, sexual dysfunction, particularly for the younger patient who is most likely to present with early hair loss, was seen in between 2.1% and 3.8% of men[10]. Initial treatment of early alopecia is typically non-invasive and the two medications approved by the FDA today are minoxidil and finasteride. For minoxidil, it is reported that approximately one-third of patients with AA respond with new hair growth[11]. In contrast, invasive transplant options are generally not offered to patients with early AA and if so, require significant financial resources. As a result, there remains a significantly large gap between these medicinal and transplant options. Hence a distinct medical need remains specific to addressing early alopecia.

During hair follicle growth (anagen), the hair follicle delves deep into the rich dermal macroenvironment as it grows to maturity where it is surrounded by large lipid-filled adipocytes. These intradermal adipocytes regenerate with faster kinetics than other adipose tissue depots and such growth parallels with the hair cycle, suggesting an interplay exists between hair follicle cells and adipocytes[12]. Thus, it has been established that adipose is an integral part of the normal hair cycle and it is hypothesized that telogen may be due to an absence of adipose tissue as it is reported that hair loss and decreased adipocytes occur together[12,13]. Therefore, the transplantation of adipose tissue, or autologous fat transfer (AFT), into the subcutaneous layer of fat in the scalp for purposes of stimulating hair growth is consistent with the reported literature that indicates hair loss and adipose loss occur in tandem.

Autologous Fat Transfer

In an AFT procedure, a patient's subcutaneous adipose tissue is aspirated from one location (most commonly the abdomen or thighs) and transferred into another depot of subcutaneous fat located throughout the body (e.g., mid-face). This procedure is reported to be practiced by physicians for over 100 years and autologous fat should be free from problems often associated with artificial materials or from allergic reactions[14]. However, AFT is not without its own limitations most significant of which is the fact that an unpredictable amount of the transferred fat can die as a result of damage during tissue harvest, processing, and implantation leading to loss of volume and a degree of unpredictability in outcome.

The process of fat transfer necessarily involves disconnecting the fat from its blood supply, implanting it into the defect, and then waiting for natural healing processes to incorporate the transferred tissue with native fat. Survival of the transferred tissue is dependent upon harvest and processing approaches that maximize tissue viability[15]. It is also dependent upon simple diffusion to supply nutrients and oxygen and to remove wastes until such time as healing processes restore its blood supply. Diffusion through a solid tissue such as fat is only effective across a distance of a few millimeters. Consequently, any transferred tissue that is more than a few millimeters away from the blood supply of recipient site tissue is at risk of dying. Loss of graft tissue from this problem is a frequent problem. Clinicians frequently overcorrect adding extra tissue in an effort to compensate for inevitable tissue loss that has been estimated at between 20-80% of the implanted tissue[16-18]. As a result of this unpredictability defect repair frequently requires multiple repeated or staged procedures performed at intervals of three or more months. For example, one large study reports up to five treatments needed (mean = three treatments) in order to achieve success in restoring volume[19]. This leads to delays in achievement of effective treatment of the defect, expense, and the higher morbidity of repeated tissue collection and implantation.

A number of investigators have evaluated ways by which the healing process can be modulated in an effort to understand and augment graft retention and, thereby, limit the number of procedures needed to achieve successful treatment. For example, animal studies have shown that use of agents that stimulate the healing process (for example, gene therapy with factors that stimulate new blood vessel growth[20]) can increase the survival of transferred tissue and that, conversely, agents that inhibit healing reduce survival[21]. Recent preclinical and clinical data have shown in addition to being a source of tissue for soft tissue filling, human adipose tissue contains cells that have the ability to promote healing[22,23]. Zhu *et al* have used an animal model to show that coating one volume of adipose tissue with cells isolated from another volume of adipose tissue results in an approximate doubling of graft retention at six and nine months[24]. This finding has been confirmed by an independent study[25]. The concept of this approach is that signals generated at the interface between implanted fat and adjacent breast fat will induce improved healing. Increasing the number of cells capable of generating these signals at this interface will lead to successful tissue retention.

In addition, Puregraft processed adipose has an excellent safety profile in aesthetic body contouring[26].

Currently, there are few, if any, minimally invasive, autologous cell therapeutic modalities being developed that address early alopecia. However, analyses from other therapeutic applications of

ADRCs and AFT suggest that a cell-enriched based approach for the treatment of early alopecia may be of significant benefit.

2.1.1 Clinical Experience with ADRCs

To date, thousands of patients have been treated with autologous ADRCs isolated using the Celution System (Cytori Therapeutics, San Diego, USA). Celution processed ADRCs have an excellent safety profile in a variety of conditions including acute myocardial injury, patients with chronic heart muscle damage, breast insufficiency following lumpectomy (a cell-enriched AFT procedure), chronic cutaneous wounds, and urinary incontinence, and most recently in a small study of scleroderma patients[27-32].

In addition, Puregraft processed adipose has an excellent safety profile in aesthetic body contouring[26].

Cytori's initial clinical experience in treating pathological conditions was in the myocardium, The PRECISE Clinical Trial evaluated the safety and feasibility of intramyocardial administration of ADRCs in patients with chronic myocardial ischemia not amenable to revascularization.[27] Clinical results at 18 months have demonstrated safety and signs of feasibility. PRECISE was a prospective, double-blind, randomized, parallel group, placebo-controlled, sequential dose escalation study which enrolled 27 subjects. Following baseline electromechanical mapping, subjects received ≤ 15 intramyocardial injections of ADRCs (n=21; median dose of ADRCs 42 x 10^6 per subject) or placebo (n=6: indistinguishable solution) in the area(s) of the heart with inducible ischemia. ADRCs were processed using the Cytori Celution System. ADRC-treated subjects demonstrated improvement in maximum oxygen consumption (VO_2max) relative to a placebo control. Adverse events and serious adverse events were equally distributed across all treatments groups with angina reported as the most frequent SAE.

The APOLLO Clinical Trial was a safety and feasibility study of ADRCs processed by the Celution System and delivered via the intracoronary route in the treatment of patients with ST-segment elevation myocardial infarction (STEMI).[28] This was a prospective, double-blind, 3:1 randomized (ADRC: Placebo), parallel group, placebo-controlled trial. A total of 14 patients were enrolled and treated according to protocol, 10 patients received ADRCs and four received placebo.

The APOLLO study demonstrated that liposuction adipose harvest for the purpose of processing and returning autologous ADRCs via the intracoronary infusion of 20 x 10^6 ADRCs can be performed with an acceptable safety profile.

Case series have described benefits in the treatment of radiation injury, fistulas and stress urinary incontinence. Yoshimoto et al. described efficacy of ADRC treatment in three patients presenting with chronic radiation injuries with ulcers and severe fibrosis.[29] They reported increases in local blood circulation at the site by ultrasound and dramatic wound healing. Gotoh et al recently described improvements in urinary incontinence following ADRC injections in a case series of 11 men who underwent radical prostatectomy.[30] Of note, enhanced ultrasonography showed a progressive increase in blood flow to the injected area in all patients. Borowski reported complete wound closure of three patients treated for long-standing cryptoglandular fistula-in-ano

using ADRCs.[31]An open label trial in 12 patients with systemic scleroderma from France examining the effects of subcutaneous administration of ADRCs to all fingers has recently been published.[32] Data at six months indicated significant improvements in Cochin score, Raynaud's severity score, and in the Scleroderma Health Assessment Questionnaire (SHAQ). The procedure was tolerated well without complications.

3 RATIONALE

For both sexes, the negative physical and psychological effects of AGA have been documented. In Stough's report, the authors indicate that while the condition may not appear to cause direct physical harm in men, hair loss can protect against sunburn, cold temperatures, mechanical injury, and ultraviolet light[3]. Beyond the physical, hair loss is known to psychologically affect the balding individual's perceptions of themselves. This is particularly true when looking at FPHL, where Cash and co-workers reported that while AA was a stressful experience for both sexes, it was substantially more distressing for women[7]. In sum, the impact of the condition should not be relegated as simply aesthetic in nature, and therefore satisfactory treatment regimens are necessary.

4 STUDY DESIGN

The STYLE Trial is a prospective, randomized, multi-center device trial intended to evaluate the safety and efficacy of the Celution and Puregraft Systems in the processing and preparation of an autologous fat graft enriched with adipose-derived regenerative cells (ADRCs) in the treatment of early alopecia androgenetica. Patients may be included if they are undergoing an elective cosmetic liposuction. Following informed consent and screening evaluations, eligible subjects will undergo pre-operative testing. Subjects will then undergo a fat harvest using local anesthesia with or without conscious sedating. Subjects will be randomly assigned to receive a fat graft cell enriched with ADRCs (available in two different doses), a fat graft without cell enrichment using a visually-matched blood saline solution (fat alone control), or a saline injection (no-fat control) in a 2:2:2:1 ratio.

While undergoing liposuction, lipoaspirate will be processed in the Puregraft System to remove the lipoaspirate of impurities and in the Celution System to isolate and concentrate ADRCs. After the liposuction is completed), patients will have, under a ring block local anesthesia (see further description below), a subcutaneous scalp injection of either Puregraft purified autologous fat or saline (no-fat control) followed by a separate second injection, of either ADRCs (available in two different doses), a visually-matched blood saline solution (fat alone control), or saline (no-fat control) in a 2:2:2:1 ratio.

All subjects will undergo clinical evaluations and laboratory testing prior to and after the procedure as outlined in *Section 9.0, Study Assessments,* and in the *Schedule of Procedures (Appendix A).*

4.1 Study Population

Subjects with documented early stage alopecia androgenetica will be evaluated for this study.

4.2 Sample Size

The STYLE Clinical Trial will have a sample size of 70 patients.

4.3 Clinical Sites

Up to eight (8) clinical centers in the United States will be selected to participate in the STYLE Clinical Trial.

4.4 Study Duration

Enrollment of subjects will occur over approximately 6 months. For each patient, the study duration will include a screening period of up to 28 days and a 52 week follow-up period. Therefore, the study duration is estimated to be 18 months.

4.5 Study Endpoints

4.5.1 Primary Endpoint

Safety & tolerability throughout 24 weeks

4.5.2 Secondary Endpoints

1. Trichograms (Hair Growth)t 24 weeks (change from baseline)
2. Trichograms (Hair Density) at 24 weeks (change from baseline)
3. Global photographs at 24 weeks (change from baseline)
4. Hair Investigator Satisfaction Survey at 24 weeks (change from baseline)

4.5.3 Exploratory Endpoints

1. Trichograms (Hair Growth)at times other than 24 weeks
2. Trichograms (Hair Density) at times other than 24 weeks
3. Trichograms (Anagen/Telogen Rate, Hair Thickness) at times other than 24 weeks
4. Global photographs other than 24 weeks
5. Hair Investigator Satisfaction Survey at times other than 24 weeks

4.5.4 Safety Endpoints

Adverse events, Serious Adverse Events, and UADEs

4.6 Inclusion Criteria

Subjects will be enrolled into this study only if they meet ALL of the following criteria:

1. Males with a diagnosis of Alopecia Androgenetica
2. Females with a diagnosis of Alopecia Androgenetica

3. Males with hair loss consistent with Grades III, IIIA, III-Vertex, IV, IV-A, based on Norwood-Hamilton Scale (Figure 1)
4. Females with hair loss consistent with Grades I-3, I-4, II-1, II-2 based on the Savin Scale (Figure 2)
5. Provide written informed consent and comply with the study requirements
6. For women of childbearing potential: Negative pregnancy test at screening visit plus willingness to maintain two forms of contraception for the duration of the study.
7. Subject is willing to maintain a consistent hair length and natural hair color, including the absence of coloring agents, during the study period.
8. Ability to complete study procedures, patient surveys, and pictures.
9. Subject is ≥ 18 years of age.
10. Body Mass Index < 40kg/m^2

4.7 Exclusion Criteria

Subjects will not be enrolled into this study if they meet ANY of the following criteria:

1. Subjects who have used minoxidil, or any oral or topical medication including over the counter and herbal medications for the treatment of hair loss within 6 months of study screening, or finasteride or dutasteride within 12 months of study screening
2. Treatment with an investigational product or procedure within 30 days or plans to participate in another clinical study
3. Subject who has previously failed or has been deemed non-responsive to a previous experimental hair loss treatment.
4. Subject must have no previous hair transplant, cell treatment, micro needling, or any other treatment in the last 6 months in the scalp.
5. Subject is currently suffering from an active autoimmune disease such as serum lupus erythematosus, or alopecia areata. Subject is currently suffering from dermatologic condition in the treatment area or has a significant scar in the hair treatment area that, in the opinion of the investigator, will make hair growth difficult (such as systemic burns, etc.).
6. History of autoimmune disease or organ transplantation or a patient on immunosuppressive medication(s).
7. Diagnosis of cancer, receiving active treatment
8. Active systemic infection
9. Requires chronic antibiotics, systemic corticosteroids
10. Use of systemic agents that increase bleeding or clotting, or disorders associated with these effects, including patients receiving GIIB/IIIa inhibitors within 2 weeks prior to the study procedure through to 1 week after the study procedure.
11. Clinically significant medical or psychiatric illness currently or within 30 days of study screening as determined by the investigator
12. Prior surgery in the treatment area
13. Any disease or condition (medical or surgical) that, in the opinion of the investigator, might compromise dermatologic, hematologic, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, or central nervous system function; or any condition that would place the subject at increased risk
14. Pregnant or lactating women or women trying to become pregnant

15. Known allergic reaction to components of study treatment and/or study injection procedure
16. Subject has any disorder that may prevent compliance to study procedures and visits
17. Subject who is part of the study staff, a family member or friend
18. Diabetes or thyroid disorder
19. Subject who has a sensitive, irritated, or abraded scalp area.
20. Women who have an alternate diagnosis that is associated with hair loss.
21. Body Mass Index < 18 kg/m^2
22. Clinically significant abnormal findings on laboratory screening panels, including hemoglobin ≤ 10 g/dL.
23. Hepatic dysfunction, as defined as aspartate aminotransferase (AST), alanine aminotransferase (ALT), or bilirubin levels > 1.5 times the upper limit of normal range (x ULN) prior to randomization.
24. Chronic renal insufficiency as defined as a serum creatinine > 1.5 mg/dL in men or > 1.2 mg/dL in women.
25. An elevated PT/PTT, INR, or platelet count < 100 x 10^9/L

5 ENROLLMENT

5.1 Subject Enrollment

Patients are considered enrolled in this study when all of the following have occurred:

1. Written informed consent is obtained
2. All inclusion criteria and no exclusion criteria have been met
3. All screening evaluations are complete

5.2 Randomization and Subject Identification

All subjects will undergo liposuction and will be randomized into one of four parallel arms in a 2:2:2:1 ratio to receive either low dose ADRCs cell enriched fat (n=20), high dose ADRC cell enriched fat (n=20), non-cell enriched autologous fat alone control (n=20), or no-fat control saline injections (n=10). Randomization will be via an interactive voice/web response system (IVRS/IWRS), or an alternatively acceptable system, and occur on the procedure day, prior to the start of liposuction.

Patients randomized into the study will be assigned the treatment corresponding to the next available number in the computer-generated randomization schedule. The dose of the test material (ADRCs or placebo) is discussed in Section 6.3.

Randomization and dose preparation will be performed by an unblinded pharmacist, or other designated qualified personnel, as outlined in the Study Reference Manual. The unblinded pharmacist or designee will not be involved in study patient care, management or follow up procedures and assessments.

5.3 Blinding Procedures and Safeguards

The following will be the "blinded parties", meaning that the listed will have no knowledge of the patient's treatment assignment:

- Patients
- Core Laboratories
- Statistician

The "**unblinded parties**", meaning those that will or may have knowledge of a patient's treatment assignment, will be the following:-

- Investigators
- Unblinded Pharmacist or designee involved in the dose preparation procedures and randomization of the patient
- Data Monitoring Committee Members

The study blind should not be broken except in a medical emergency (where knowledge of the test material received would affect the treatment of the emergency) or regulatory requirement (e.g., for SAEs or death).

If unblinding becomes necessary, the Investigator should notify the Sponsor or the Medical Monitor as soon as possible. If the blind is broken, the date, time and reason must be recorded in the Subject's electronic case report form (eCRF), together with a note of a protocol violation if applicable, and any applicable reports [e.g. Adverse Event (AE)].

5.4 Subject Withdrawal and Replacement

Subjects may withdraw from the study at any time and for any reason without penalty or prejudice to his or her future medical care. If a subject is prematurely withdrawn from the study for any reason, the reason(s) for withdrawal must be recorded in the Subject's source documentation and on the eCRF.

The Investigator must make every effort to perform the Early Termination evaluations. This visit shall take place as soon as possible after it is determined that the Subject will be withdrawn from the study and will comprise the observations and procedures scheduled at the next visit.

6 CELUTION & PUREGRAFT SYSTEMS

6.1 Celution& Puregraft System Descriptions

The Celution System consists of a stand-alone re-useable hardware unit called the Celution Device, the Celution Consumable Set, and Celase®. The Celution System prepares an ADRC output from adipose tissue collected by standard liposuction techniques.

Following the collection of tissue, the adipose tissue is introduced into the device's collection canister in order to wash the adipose tissue and remove deleterious substances (such as cellular debris)(Detailed instructions for use are found in the *Celution User Manual, the Celution Consumable IFU and the Celase IFU*).

The Puregraft 50 System is a sterile, single use, closed system intended for the preparation and delivery of autologous fat grafts back to the same patient for cosmetic and reconstructive surgery applications. The dual filtration bag system utilizes its swabable luer activated valves to connect to an off-the-shelf sterile luer lock syringe and its attached slider is used to facilitate the movement of liquids through the filter mesh and out of the Puregraft bag through the drain stub as waste. Detailed instructions for use are found in the Puregraft IFU).

6.2 Device Characterization and Intended Use

In combination with the Puregraft 50 System, the Celution System (Celution Device, Celution Consumables Set, and Celase reagent) is intended to digest adipose tissue in order to further extract, wash and concentrate adipose derived regenerative cells (ADRCs) intended for combination with autologous fat and reimplantation subcutaneously into the scalp for investigational use in the STYLE clinical trial.

The Puregraft 50 System is intended to process and purify adipose tissue to be combined with concentrated stromal stem cells and other associated progenitor cells intended for autologous implantation subcutaneously into the scalp for investigational use in the STYLE clinical trial.

6.3 Contraindications

1. Non-autologous use is contraindicated
2. Use of any tissues other than adipose is contraindicated

6.4 Intended Clinical Performance

The Celution System is designed to process lipoaspirated tissue and separate ADRCs from adipose tissue by enzymatic disassociation of the tissue and using buoyancy differences to separate the ADRCs from lipid containing adipocytes at the point of care. When ADRCs are prepared using the Celution System, the resultant cell suspension contains all of the components naturally occurring in the native tissue. Preparation of autologous ADRCs for subcutaneous delivery using the Celution System involves no cell culture and can be prepared and re-implanted into the same patient within three hours from completion of lipoaspiration.

The total viable cell count and percentage viability for each sample will be used as the acceptance criteria. This will be assessed for each patient to decide whether the cell output is acceptable, and to prepare the prescribed dose. The viable cell count will be performed by the commercially available NucleoCounter® Automated Cell Counting System. Using a small sample of the Celution System output, the NucleoCounter Automated Cell Counting System provides a count of both live and dead nucleated cells in the total sample. All personnel involved will be trained according to standardized procedures and work instructions. Cytori has performed characterizations of the live cell output obtained by the Celution System and this is consistently

70% viability or greater. This sample count is used to calculate the total number of live nucleated cells from the total preparation, to arrive at percentage of viable cells that are available for introduction into the patient.

The Puregraft System is designed to prepare purified lipoaspirate. This purification involves the near complete removal of free lipid, RBCs, and WBCs. All personnel involved will be trained according to standardized procedures and work instructions.

6.5 Celution& Puregraft System Output; Physical, Chemical, and Pharmaceutical Properties of ADRCs

The output of the Celution System is an ADRC output obtained from autologous lipoaspirate tissue. The suspension of viable ADRCs has been characterized with an average viability of >70% and the average yield is 3.24 x 10^5 ± 1.48 of mononuclear cells per gram of adipose tissue entered into the Celution System. An index of regenerative cell potential, the CFU-F assay, shows that 1.51% of those ADRCs form colonies (mean range of 0.13 to 4.08% colony forming units).

The product is a suspension of cells in a diluent. The cellular components of the suspension are made up of nucleated and non-nucleated cells. The non-nucleated cells are red blood cells (RBC) that comprise > 95% of the total cell suspension. The nucleated cells make up approximately 0.1 – 5% of the total cell suspension. Nucleated cells are present in the following approximate minimum percentages: CD 31^+, CD 34^+ (> 2%); CD 34^+, CD 31^-, CD 45^- (> 10%); CD 45+, CD 31-, CD 34- (> 15%). The combination of these three phenotypes will account for greater than 90% of nucleated cells in the product. Table 1 summarizes the ADRC cellular suspension processed by the Celution System.

Table 1. ADRC cellular suspension components and concentrations

Cell Type	Phenotype	Relative Identity of Nucleated Cell Population	% of total cell suspension
Non-nucleated Cells	Red Blood Cells		> 95%
Nucleated Cells	CD 31+, CD 34+	> 2%	0.1-5%
	CD 34+, CD 31-, CD 45-	> 10%	
	CD 45+, CD 31-, CD 34-	> 15%	

Puregraft 50 System

The Puregraft 50 System is used in conjunction with a lipoplasty device (user supplied) and does not contact the patient as it does not connect to vacuum. The Puregraft 50 System is only used on the back table in the operating room to rinse and filter an adipose tissue graft and prepare the graft for eventual injection back into the same patient during the same surgical procedure. The Puregraft 50 System is a bag with two tubing stubs/ports (tissue and drain) and is designed to harvest, rinse and filter the adipose tissue, and subsequently drain excess rinse solution away

from the adipose tissue. The rinsed and filtered adipose tissue is then removed from the Puregraft bag using syringes (user supplied) and ultimately transplanted back into the same patient. The Puregraft 50 System includes a slider tool that is attached to the exterior of the Puregraft bag. The slider is used to compress the Puregraft bag as a means to facilitate the movement of liquids through the filter mesh and out of the Puregraft bag through the drain stub/port as waste.

6.6 Proposed Mechanism of Action of Cell Enriched Autologous Fat Grafts

The proposed mechanism of action of autologous fat grafts enriched with ADRCs prepared with both the Puregraft and Celution Systems is postulated to be follicular niche stimulation. This stimulation is believed to occur through modulation of inflammation, promotion of angiogenesis and prevention of cell apoptosis. Studies suggest that cell enriched autologous graft therapy changes the inflammatory response and augments the regenerative response. Studies have detected significant amounts of paracrine growth factors, which have been shown to facilitate vascularization, and as well as those associated with anti-inflammatory effects, thereby, ameliorating injury by proinflammatory cytokines. Viability characterization of ADRCs as described above in addition to pre-clinical animal data from Cytori and other published reports support this hypothesis.

7 STUDY TREATMENTS

Subjects will be randomized 2:2:2:1 to active treatment (autologous fat enriched with ADRCs), autologous fat alone control, or no-fat control as follows:

Active (0.5×10^6 ADRCs/cm^2 scalp):	20 Subjects
Active (1.0×10^6 ADRCs/cm^2 scalp):	20 Subjects
Autologous fat alone control:	20 Subjects
No-fat control (saline)	10 Subjects

The study treatment will be administered as subcutaneous injections of either fat or saline into the subcutaneous fat layer of the scalp (40cm^2 of scalp) of each subject. Each square centimeter of scalp will be injected with 0.1 mL of purified autologous fat or saline followed by separate injection of either low or high dose ADRC injection per cm^2 scalp, or saline (fat alone control and the no-fat control). To account for the variability seen in advanced grades of hair loss (Norwood Grade II and IV), treatment areas will be focused in the mid-scalp and crown (vertex). The leading edge of hair loss will not be treated, including the peri-orbital region as fat grafting in the peri-orbital region has been associated with higher-risk complications.

7.1 Product Description – Cell-enriched autologous fat

The active treatment used for the STYLE Trial will be cell-enriched autologous fat obtained from the study subject's own adipose tissue which is prepared using the Puregraft and Celution Systems.

The excipients in the cell suspension are composed of residual Celution System reagents and diluent. Specifically, the residual reagents are collagenase (<0.005 Wünch Units/mL) and thermolysin neutral protease (< 30 caseinase Units/mL). The diluentis Lactated Ringers solution (USP).

Adipose tissue processing is detailed in both the *Puregraft* and *Celution System Users Manuals*. Preparation of the active study treatment is provided in *the Study Reference Manual*.

7.1.1 Active Treatment Dose Control

Autologous adipose purified with the Puregraft System can be readily removed directly with a sterile 1mL syringe to obtain a volume of 0.1mL for injection.

ADRC Cell count and viability will be controlled using the NucleoCounterAutomated Cell Counting System (Enfield, CT) at each site using the following acceptance criteria:

- Nominal cell count: 40 x 10^6 ADRCs
- A minimum cell count within 50% of the nominal cell count is required (i.e., a dose as low as 20 x 10^6 ADRCs is acceptable if 40 x 10^6 ADRCs is not be available)
- Cell viability: ≥ 70%

  If cell viability is <70%, as determined by the NucleoCounter Automated Cell Counting System, the subject will not be treated.
- Negative result in Gram stain testing (see *Section 7.3*)

7.2 Product Description – Control Doses

The fat alone control dose will be purified autologous tissue prepared by the Puregraft System that is not enriched with ADRCs but with saline. The amount of fat injected will be 0.1 mL/cm^2 of scalp. The fat alone control dose will also include injection of a saline solution which is mixed with 0.1mL to 0.2 mL of the study Subject's own freshly drawn blood to achieve a dilution that is visually indistinguishable from ADRCs. The saline injection of the fat-alone control must test negative in a Gram stain test of sterility prior to being administered (see *Section 7.3*). Preparation of the fat-alone control dose is provided in *the Study Reference Manual*.

The no-fat control dose will be 0.1ml/cm^2 of scalp of saline injected (delivered by a blunt tip cannula) followed by a second matching dose of saline solution (via a 25G needle) to 0.1ml/cm^2 of scalp.

7.2.1 Justification of Control Dose

To reduce the risk of bias (selection bias, performance bias, detection bias and attrition bias), all patients will undergo pre-specified screening procedures, fat harvest, and injection of active treatment or placebo. The justification and rationale of the placebo dose arm include:

1. In the presence of a concurrent placebo control group, demographics and patient selection is more likely to be balanced allowing for more reliable interpretation of study results.

2. Minimize the potential of the Hawthorne effect creating a positive impression of efficacy that may overstate the actual treatment effect.

7.3 Study Treatment Pre-Injection Sterility Testing

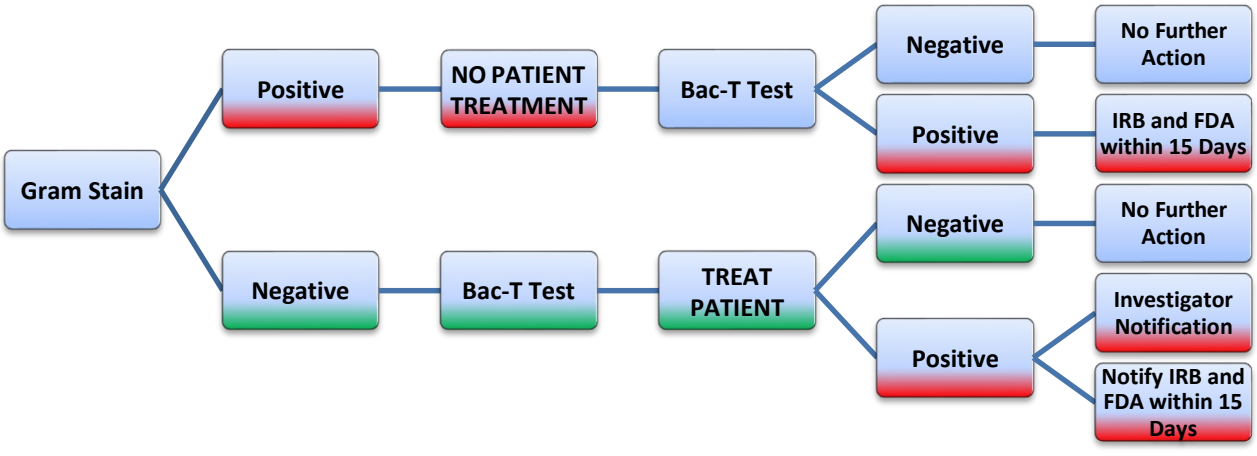
Following cell processing in the Celution System, sterility testing will be performed as described below and more fully in the *Study Reference Manual*.

A negative Gram stain test result is required prior to injection of ADRCs and/or fat alone control. A negative Gram stain test result is not required prior to injection of saline in the no-fat control arm. If the sample is determined to be positive for bacteria then the cellular administration procedure must be stopped and the subject should not receive any study treatment.

Further testing (BacT Alert Culture and Sensitivity) will be performed in order to test for the presence of any low level microbial contamination that might not be apparent in the gram stain test. Should a culture be deemed positive for microbial activity, the investigator will be immediately notified. The study patient will be evaluated and a course of treatment and/or antibiotics may be administered, as determined by the study investigator. The source of the contamination will be evaluated as appropriate. The FDA and IRB will be notified within 15 days of the investigator being made aware of any positive test results.

The following flow chart describes the activities associated with positive or negative outcomes in these two tests of sample sterility.

Figure 3: Sterility Testing of ADRC and Fat Alone Control Samples



7.3.1 ADRC Characterization

In order to characterize the phenotype of ADRCs obtained from patients with alopecia androgenetica, adipose tissue will be obtained during the elective cosmetic liposuction.; up to 360 mL of this tissue (maximum that can be processed by Celution Device) will be used to prepare the active study treatment (ADRCs) using the Celution System. Once it is determined that the cell dose has been achieved according to criteria described in *Section 7.1.1,* any remaining adipose tissue may be shipped to an outsourced facility of the Sponsor (if within two hours of the outsourced laboratory) according to procedures outlined in the *Study Reference Manual*.

In the Sponsor's outsourced contract laboratory, ADRCs will be prepared from collected adipose tissue using the same Celution System as used in the clinic and the cell output characterized using colony forming unit – fibroblast (CFU-F), a measure of the number of adipose stem cells, and multiparametric flow cytometry analyses used to define the major non-progenitor cell populations in ADRCs. In the flow analyses ADRCs will be stained using antibodies directed to CD31, CD34, CD136 and CD45 proteins. Based on the expression of these four markers, the major populations will be defined as follow:

Leukocytes	CD45+
Endothelial Cells	CD34+/CD31+/CD45-
Stromal Cells	CD34+/CD31-/CD45-
Mural cells	CD34-/CD31-/CD45-/CD146+

If sufficient cells are available, additional characterization of subpopulations will be performed using antibodies such as CD3, CD14, CD19, and CD16/56.

8 STUDY ASSESSMENTS

All assessments will be conducted at specific time points as outlined in this section and in the Schedule of Assessments in *Appendix A*.

8.1 Medical History, Physical Examination & Vital Signs

A complete medical history will be collected at the Screening Visit and will include demographic information as well as current and past medical conditions. Updated medical history information is to be collected at the Day -1 including any event that has occurred since the Screening Visit that could be considered an adverse event. Any adverse event that occurs after the ICF is signed and prior to administration of the study drug is to be recorded as an update to the Medical History.

Physical examinations should be based on the following body systems: general appearance, head (ear, eyes, nose and throat), cardiovascular, respiratory, abdomen, musculoskeletal, neurological, lymph nodes, and skin. Vital signs to be obtained include the following:

- Blood pressure (systolic and diastolic; mm/Hg)
- Heart rate (beats per minute)
- Body temperature (°F)
- Respiration rate (per minute)

8.2 Hair & Scalp Evaluation Assessments

The physical status and satisfaction of the subjects' scalp and hair will be evaluated using several assessment tools. The assessment tools are listed below and detailed information and instructions provided in the *Study Reference Manual*.

- Hair Investigator Satisfaction Survey
- Patient Satisfaction Survey
- Trichogram analysis
- Global photography

8.3 Prior and Concomitant Medications

Any medication a subject receives is considered a concomitant medication, and must be recorded in the subject's source documentation throughout the study. All concomitant medications will be recorded in the eCRF from 90 days prior to screening through 24 weeks post procedure.

Information to be recorded on the eCRF will include: generic medication name, route of administration, dosage, indication, start date, and stop date. Medications used as part of the liposuction and injection procedure do not need to be recorded in the eCRF but should be recorded as part of the operative records. As needed analgesic medications will be recorded by the subject's in a daily medication diary for the 14 days immediately preceding the next study visit.

8.3.1 Prohibited Medications

Subjects should not receive the following medications:

- Minoxidil, or any oral or topical medication including over the counter and herbal medications for the treatment of hair loss within 6 months of study screening, or finasteride or dutasteride within 12 months of study screening
- Treatment with an investigational product or procedure within 30 days of study screening
- Systemic steroids exceeding prednisone 10 mg daily (or equivalent)
- Biologic agentsor immunosuppressive medications within 90 days of the Screening Visit

If treatment with any prohibited medication becomes necessary during study participation, the subject will be discontinued from the trial.

8.4 Laboratory Procedures

All laboratory assessments will be performed locally at each center's laboratory by means of their established methods (using site specific laboratory normal values). Blood and urine samples should be taken using standard techniques and samples should be stored and shipped according to the laboratory guidelines.

8.5 Adverse Events

Adverse events will be recorded Starting on Day 1, immediately after study procedure has started and through to the End-of-Study (Week 24), Any adverse events experienced between signing the ICF and prior to administration of the study drug will be recorded in the medical history. See *Section 12* for more information pertaining to recording of adverse events.

9 STUDY VISIT REQUIREMENTS

The Schedule of Procedures is outlined in Appendix A.

9.1 Screening (within 28 to 7 days prior to procedure)

Subjects will undergo the following screening procedures:

- Written informed consent
- Inclusion and exclusion criteria evaluation
- Medical history
- Prior and concomitant medications
- Physical examination
- Laboratory Tests
    - CBC with Platelets
    - Electrolytes, alkaline phosphatase, bilirubin, AST, ALT, BUN, Creatinine
    - PTT, PT/INR
- Vital signs
- Pregnancy test (urine) for female patients of child-bearing potential
- Evaluation of suitability for fat tissue harvest and liposuction procedure(see *Section 9.3.3.1*)

The following tests are to be performed:

- Global Photography
- Trichogram with tattooing

9.2 Pre-Operative Procedures (Day -1; performed within 24 hours of the liposuction)

- Confirm inclusion/exclusion criteria
- Physical Examination
- Vital Signs
- Assessment for Adverse Events
- Concomitant Medications
    - Collect daily medication diary completed for 14 days immediately preceding visit
- Laboratory Tests
    - CBC with Platelets
    - Electrolytes, alkaline phosphatase, bilirubin, AST, ALT, BUN, Creatinine
    - PTT, PT/INR

- Pregnancy test (urine) for female patients of child-bearing potential

93 Procedure Day (Day 1)

9.3.1 Fat Harvest

9.3.1.1 General requirements

- Fat harvest will be performed on the day of treatment as part of an independent, elective cosmetic liposuction.
- Fat harvest planning should include assessment of patients general health condition to undergo the procedure
- Standard tissue calipers or expert plastic surgical examination should be used to assess possible body sites for subcutaneous fat tissue. Patients should have greater than or equal to 2 cm of subcutaneous fat tissue available in each contemplated area to be suitable for liposuction
- Prepare up to 3 sites, including the preferred abdomen and flanks along with the inner and the outer thighs and the posterior and anterior thighs. To estimate harvestable fat from the harvest site the following guideline may be used: Estimated fat from the harvest site = volume of the site/8 = length of the marked skin x width of the marked skin x height (i.e. caliper skin-fold thickness) / 8. All patients who have inadequate fat deposits (i.e. < 200 ml of lipoaspirate from 3 bilateral sites) are to be excluded from the study. Any patient with an area of active skin infection in the site of lipoharvest will be excluded from the study.
- As noted elsewhere in this protocol, fat harvest should NOT be performed on patients who have received any anticoagulant within 1 hour of liposuction, substantial anticoagulation (e.g.: GIIb/IIIa inhibitor class drugs) within the two weeks prior to fat harvest, or who have an abnormal aPTT.
- Fat tissue should be obtained under sterile technique using local anesthesia with or without conscious sedation. General anesthesia should not be used.

9.3.1.2 Fat Harvest Procedure

Fat harvest from small volume liposuction is a standard procedure practiced by trained physicians in a variety of settings and using a variety of techniques. However, a specific set of guidelines have been established for the collection of fat that can then be used for the optimized preparation of ADRCs. These guidelines, which are recommendations and not requirements, include the following;

- Syringe-based fat harvest is preferred.
- Use up to 32 cm long, 3-5 mm inner diameter Toomey cannula with a standard tip
- 60 mL Toomey syringes are used for tissue acquisition
- Use 14 gauge, up to 30 cm, blunt LAMIS infiltrator for tumescent fluid administration
- Symmetric fat removal is required keeping the overall area of aspiration as small as possible

- The abdominal region is the preferred site for fat harvest

1. Local anesthesia with or without conscious sedation; general anesthesia is not permitted for fat harvest
2. Using sterile technique, prepare up to 3 sites, including the preferred abdomen and flanks along with the inner and the outer thighs and the posterior and anterior thighs.
3. Make an approximately 0.5 cm stab skin incision
4. Infiltrate tumescent solution using a blunt LAMIS infiltrator and a volume ratio of 1:1 of tumescent solution to fat to be harvested

Tumescent fluid formula:

- 500 mL of Lactated Ringers solution
- 20 mL of 1% Lidocaine
- 1 mg of epinephrine

5. To sufficiently induce vasoconstriction/hemostasis during the liposuction procedure a minimum of 500 mL of tumescent fluid must be used.
6. After approximately **10 minutes**, the adipose tissue is harvested through the same incision, using the aspiration cannula attached to the Toomey syringe
7. After the syringe is filled (complete filling is not required), cap syringe and replace with empty one
8. Continue fat harvest until desired volume is safely achieved, with the target volume of adipose tissue harvested limited to approximately 450 mL
9. Fat harvest will be limited to areas where tumescent fluid has been infiltrated
10. Vital signs are monitored continuously during liposuction procedure
11. Close surgical incision with appropriate suture
12. Apply pressure bandage immediately upon conclusion of tissue harvest

NOTE: Approximately 0.5 mL blood must be drawn and delivered to the unblinded staff prior to dose preparation. The blood will be used to prepare the fat alone control (see Section 7.2).

9.3.1.3 – Fat Harvest Stopping Rules

The physician performing the fat harvest procedure should continuously monitor the patient for signs of significant bleeding from the puncture site(s) and overall hemodynamic stability. The liposuction procedure should be terminated if any of the following occur:

1. Drop in systolic blood pressure < 90mm/Hg that is unresponsive to volume or pressor support
2. Profuse or uncontrollable bleeding from the puncture site(s)
3. Rapid expansion of subcutaneous space at the liposuction site(s) related to bleeding into the subcutaneous space
4. Hemoperitoneum or pnuemopertinoeum
5. Hemothorax or pneumothorax
6. Evidence of perforation of a vascular structure that requires ligature or surgical control

7. Evidence of perforation into abdominal cavity, peritoneum or gastrointestinal organ

Should any of the above occur, the fat harvest procedure should be terminated and the patient treated according to standard of care. DO NOT PROCEED WITH INJECTION. Complete the study specific SAE form and notify the sponsor within 24 hours.

9.3.2 Between Fat Harvest and ADRC Injection

Vital signs will be monitored continuously between the fat harvest and cell injection procedures.

9.3.3 Fat + ADRC Injection

The following procedure is recommended for subcutaneous injection into the scalp for the treatment of baldness due to alopecia androgenetica:

Autologous Fat & Saline Injection
This fat or saline injection procedure will occur after the completion of the liposuction. Aseptic technique should be maintained throughout the procedure. A treatment grid will be prepared in the area to be treated. The grid is a piece of silicone rubber that is placed on the scalp of the subject in the desired position and a surgical skin marker is used to mark each of the holes which are spaced every centimeter. The recipient site is anesthetized using a local ring block with 1% lidocaine with 1:100,000 epinephrine. Aliquots of 0.2mL should be injected in a circular ring fashion and the dosage should be adjusted according to the response of the patient and the site of administration. The lowest concentration and the smallest dose producing the required effect should be given. The maximum dose delivered should not exceed 7mg/kg. Sedation may be employed to minimize patient discomfort at the discretion of the investigator. Tissue from the Puregraft 50 is prepared in separate, sterile 1mL luer lock syringes, and an 11-blade scalpel can be used to make a stab incision (incision is made at a strategic insertion point to facilitate access to the area to be treated) to allow insertion of a 0.9mm-1.2mm diameter blunt-tip cannula. This cannula is then inserted into the subcutaneous adipose tissue plane and the tip is fanned into each 1 square centimeter grid to deliver 0.1mL of tissue or saline (no-fat control).

ADRC & Saline Injection
After preparation of the ADRCs, either the low or high dose of ADRC or saline will be injected using a 25G needle directly through the skin into the layer of subcutaneous adipose using the identical grid markings made in the paragraph described above. Additional local anesthesia ± sedation may be applied as deemed necessary by the investigator.

A summary of the clinical workflow is described in Appendix C.

9.4 Immediately Post-Injection (Day 1)

- Vital Signs will be monitored for one hour following the injection procedure
- HGB/HCT blood level will be evaluated

- Assessment of injection and fat harvest site
- Overall physical assessment

9.5 Post-injection Follow-up visits (Week 1)

- Physical examination
- Vital Signs
- Assessment for Adverse Events

9.6 Post-injection Follow-up visits (Weeks 6, 12, 24, and 52)

- Physical examination
- Vital Signs
- Assessment for Adverse Events

The following tests are to be performed:

- Subject questionnaire
- Global photography
- Hair Investigator Satisfaction Survey

A summary table of all follow up evaluations is outlined in Appendix B: Schedule of Procedures

9.7 Early Termination Evaluation

Subjects that discontinue early from the study, unless consent is withdrawn, shall have an Early Termination (ET) evaluation. This visit shall take place as soon as possible after it is determined that the Subject will be withdrawn from the study.

If the ET Visit occurs prior to the Week 24 visit the observations and procedures for the ET Visit are the same as those required at the Week 24.

The reason for early withdrawal must always be clearly documented in the Subject's source documentation. Contact with the Subject must be attempted to determine overall health status, and contact details must be documented in the Subject's source documentation. If lost to follow-up, details of three contact attempts must be documented in the Subject source documentation and every effort must be made to determine if the Subject has expired.

10 RISK/BENEFIT ANALYSIS

10.1 Risks

The use of adult regenerative cells from adipose tissue and other sources has shown improvement in muscular (cardiac) function after injection into ischemic areas of the heart. The PRECISE Clinical Trial has shown an acceptable safety profile and signs of benefits following intramyocardial administration of ADRCs processed by the Celution System. Every potential complication of ADRC injections are unknown at this time; however injection of cells from adipose tissue have been delivered with guided intramyocardial injections with no clinical significant sequelae. A clinical trial of 12 patients with hand dysfunction and pain from scleroderma followed for 6 months showed minor adverse events related to subcutaneous injection, typical liposuction adverse events, and no adverse events directly related to ADRCs.

10.1.1 Subcutaneous Delivery Risk Analysis

Risks involved with subcutaneous delivered adipose plus cells include:

- Hematoma or bleeding
- Infection
- Inflammation, rash, or papules at the injection site
- Nerve injury, pain, paresthesias or sensory disturbances
- Diminished function
- Shock loss

Direct intramuscular injections of Celase has been carried out in rodent models showing a margin of safety of greater than 10 for injection of Celase into the heart muscle. In addition, intra-ventricular applications of ADRCs into rat hearts during efficacy studies did not result in adverse events over 12 weeks of follow-up. Further, as noted above, 21 patients treated by direct injection into the muscle of the heart in the course of the PRECISE study exhibited no adverse events associated with ADRC injection In addition, a study of 12 patients with subcutaneous injection in the fingers of patients with scleroderma showed minor adverse events and no serious adverse events.

10.1.2 Subcutaneous Injection Risk Management

Investigators and all study personnel will be trained in the details of all aspects of the study procedures. To minimize risks and increase the chances of a favorable clinical outcome the following measures are required:

- Enrollment of Subjects who qualify per the inclusion/exclusion criteria in the protocol
- Strict adherence to the study protocol
- Use sterile technique throughout the procedure
- Use standard of care for the monitoring of and treatment of possible adverse events following injection procedure

10.1.3 Celution & Puregraft System Risk Analysis

The investigators and all study personnel will be trained in the details of all aspects of the study procedures relevant to their particular area of responsibility.

- Train investigators and all study personnel in the details of the operation of the Celution & Puregraft System.
- Inspect the package integrity and sterility indicators on all disposables used with the devices and maintain sterility of the fluid paths.
- Follow Instructions for Use for the Celution & Puregraft Systems, including all warnings, precautions and contraindications.

10.1.4 Overall Study Risk Management

The following measures implemented by Kerastem will minimize the risks associated with patients' participation in clinical studies:

- Kerastem selects personnel (Kerastem employees, agents, licensees, and clinical investigators at the sites) with extensive experience in conducting clinical studies and in performing procedures involved in the protocol including fat harvest and procedures involving the hands
- All examinations, treatment procedures, and interpretation of clinical data generated during the study is directed, overseen and analyzed by an appropriately licensed and credentialed physician who has been trained to the clinical study protocol.
- Kerastem developed the clinical protocol and training programs to ensure that the study personnel at Kerastem and at the clinical sites have a strong knowledge and understanding of the clinical protocol, including patient selection criteria and procedure requirements.
- Kerastem will ensure that the investigators are trained to the procedure requirements in the protocol, and the Instructions for Use for the Celution and Puregraft Systems.
- Kerastem carefully developed patient eligibility criteria for the investigation including clearly defined inclusion and exclusion criteria to ensure that only properly selected patients will be enrolled in the clinical study.
- The protocol is designed so that patient treatment and follow-up procedures will be consistent with those of the clinically established standard of care.

10.1.5 Fat Harvest Risk Analysis

The risks of standard small volume liposuction in healthy patients are known and are minimal and recovery is usually fast. Following standard liposuction the following effects can be expected:

Common

- Edema and redness of the liposuction areas for a few days
- Moderate contusion of the liposuction areas for a few months
- Uncommon
- Persistent edema

- Persistent bleeding
- Hematoma
- Visible puncture sites

Rare

- Infection
- Deep Vein thrombosis (DVT)
- Persistent bleeding requiring transfusion

10.1.6 Fat Harvest Risk Management

The Investigators and all study personnel will be trained in the details of all aspects of the study procedures. Standardization of fat harvest techniques is critical to a good clinical outcome. To minimize risks and increase the chances of a favorable clinical outcome the following measures are required for the liposuction procedure:

- Performed by an appropriately licensed and credentialed physician
- Monitoring of vital signs throughout the procedure.
- Sterile technique is followed throughout.
- The adipose tissue is handled gently at all times.
- HGB, HCT prior to and 1-2 hours post-procedure
- To sufficiently induce local vasoconstriction/hemostasis during the fat harvest procedure, a minimum of 500 mL of tumescent fluid is used containing:
    - 500 mL of Lactated Ringers solution
    - 20 mL of 1% Lidocaine
    - 1 mg of epinephrine
- A blunt 14 to 16 gauge LAMIS infiltrator (or equivalent) will be used for infiltration with tumescent solution
- After ~10 minutes, the adipose tissue may be harvested through the same incision, using the aspiration cannula attached to a syringe
- A blunt cannula with a minimum inner diameter of 3 mm is preferred for lipoaspiration.
- Lipoaspiration is recommended to be done manually using a syringe (60 mL Toomey syringe is preferred).
- Enrollment of only patients who qualify per the inclusion / exclusion criteria defined in the protocol) including screening blood work
- Strict adherence to the study protocol
- Standard of care for the monitoring of and treatment who experience any adverse event for liposuction
- Target volume of adipose tissue is limited to approximately 450 mL
- Close surgical incision with appropriate suture
- Apply pressure bandage immediately upon conclusion of tissue harvest

Fat harvest should <u>NOT</u> be performed on patients who have received any anticoagulant within 1 hour of the procedure, substantial anticoagulation (e.g.: GIIb/IIIa inhibitor class drugs) within two weeks prior to fat harvest, or who have an abnormal PTT.

10.2 Potential Benefits

This clinical investigation is designed as a safety and efficacy study. Therefore, it is not known at this time whether any direct subject benefit can be expected. Given the proposed mechanism of action of autologous adipose enriched with or without ADRCs, we expect there may also be a beneficial effect in the treatment of baldness due to alopecia androgenetica. Previous ex-US patient experience with similar inclusion/exclusion criteria documented encouraging positive efficacy results and a favorable benefit to risk profile (abstract accepted at 2014 International Federation of Adipose Therapeutics and Science (IFATS) Annual Meeting-November 2014).

11 STATISTICAL METHODS AND DATA ANALYSIS

This is a multi-centre, single-blinded, randomized, parallel group, controlled study to evaluate the preliminary safety of cell-enriched autologous fat compared to placebo in patients with baldness due to alopecia androgenetica. The primary endpoint will be the safety and tolerability of the procedure.

An analysis of covariance (ANCOVA), with the baseline measure used as a covariate, will be used for the analyses of the secondary efficacy endpoints. Comparisons of each active arm with placebo will be made using Dunnett comparisons. The ITT population will be used for the primary analysis; the analysis will also be performed in the PTE population and will be considered as supportive of the ITT analysis.

11.1 General Considerations

All statistical tests will be two sided, and statistical significance will be assessed with respect to a nominal p-value of 0.05. Before the first data review meeting of the DMC is held, a separate statistical analysis plan (SAP) will be completed, providing detailed methods for the analyses outlined in the following subsections. The SAP will detail all planned analyses and will serve as a statistical programming requirements document.

11.2 Determination of Sample Size

The sample size for the trial has been set at 70, based on clinical considerations and is not based on formal power calculations.

The objective of the STYLE Trial is to assess the safety and preliminary efficacy of cell-enriched autologous adipose delivered via a subcutaneous route in the treatment of baldness due to alopecia androgenetica. As the primary endpoint is safety and tolerability, the investigators believe that a sample of 20 subjects per arm and a 10 patient no-fat saline control is adequate.

11.3 Data Analyses

Safety and efficacy endpoints will be summarized by treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum), for quantitative variables and frequencies and percentages for categorical variables. Laboratory data will also be summarized using shift tables

between before procedure and at Day 1, post procedure, with values categorized as less than lower limit of normal range, within normal range, and above upper limit of normal range.

For quantitative efficacy variables, summaries will be provided at each post-baseline visit time point. Additionally variables will be analyzed using ANCOVA models with adjustment for the baseline value of the variable.

Related adverse events will be analyzed separately for those related to ADRCs and the delivery of ADRCs (i.e., injection site such as shock loss). A separate safety analysis will be performed for Adverse Events of Interest (Appendix B, Adverse Event Terminology and Grading).

11.3.1 Primary Endpoint Analysis

The primary endpoint for the study is safety and tolerability through 24 weeks

The hypotheses are:

> Adverse event rates through 24 weeks for active treatment will be less than or equal to adverse events rates published for autologous fat grafting.
>
> Vital sign abnormalities through 24 weeks for active treatment will be less than or equal to those published for autologous fat grafting.
>
> Physical exam abnormalities through 24 weeks for active treatment will be less than or equal to those published for autologous fat grafting.

The corresponding null hypotheses are that the adverse event rates will be greater for active treatment arms than for placebo.

Statistical testing will not be performed for these hypotheses, but the safety endpoints will be evaluated clinically.

11.3.2 Secondary and Exploratory Endpoint Analysis

The secondary endpoints are change from baseline in the (a) Average Trichogram growth rates at 24 weeks, (b) Average Trichogram density rate at 24 weeks, and (c) global photographs at 24 weeks and (d) hair Investigator Satisfaction Survey at 24 weeks. Multiplicity adjustment will not be made when testing the three secondary endpoints.

Exploratory endpoints are listed in Section 4.5. As these are exploratory, p-values for each analysis will not be corrected for multiple comparisons. These analyses will provide evidence concerning the safety of effectiveness of the product.

11.3.3 Subgroup Analysis

Statistical analysis of efficacy and safety endpoints will be performed in the total group.

11.4 Background, Demographic Analyses

Demographic data, medical history, concomitant disease will be summarized by means of descriptive statistics (n, mean, SD, median, minimum and maximum) or frequency tables, stratified by treatment.

11.5 Subject Disposition & Analysis Populations

Reasons for withdrawal post-randomization will be summarized.

The treatment analyses will be performed on intent-to-treat basis as well as on a per-treatment-evaluable basis, as defined below:

Safety: All treated subjects; subjects will be analyzed as treated.

Intent-to-Treat (ITT): All randomized subjects; randomization will occur on procedure day prior to liposuction. Subjects will be included in the analysis as randomized

Per-Treatment-Evaluable (PTE): All randomized subjects who have received treatment and follow-up information is available. Protocol violators, where the violation is judged to affect the interpretation of the treatment effect will be excluded. All exclusions will be made prior to the breaking of the treatment blind.

11.6 Handling of Missing Data

Safety data will not be imputed.

PTE data will not be imputed.

Missing efficacy data will be imputed for the ITT analysis population. For missing data caused by worsening of scleroderma (either hand or systemic manifestation), the missing value will be replaced by the least favorable observation from the prior Visits excluding baseline. For other missing data, last observation carried forward will be the primary method of imputation. As a sensitivity analysis, multiple impute ion methods (SAS PROC MI and PROC MIANALIZE) will be used.

For the analysis of quality of life, missing responses to individual questionnaire items will be imputed using the methods prescribed by the questionnaire vendor.

11.7 Protocol Deviations

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as “minor” or “major” in cooperation with the Sponsor. Deviations will be defined prior to un-blinding. Major deviations may result in removal from the PTE analysis population.

11.8 Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will be comprised of medical specialists and a biostatistician who are not participants in the study. The DMC will be provided with all safety data as well as efficacy data for the primary and secondary endpoints in order to fully

evaluate the benefit to risk profile of the study procedures. The DMC will be responsible for the review of the data and generate recommendations on the conduct of the trial.

The DMC will be asked to review data and generate recommendations after 10, 20 and 40 subjects have at least 1 week of follow-up.

11.8.1 Adverse Events Initiating Safety Review

The Sponsor is to be informed of the following adverse events within 24 hours of the site becoming aware of the event:

- Gangrene of the scalp in two (2) or more within fourteen (14) days of the procedure
- Infection of the scalp requiring hospitalization and intravenous antibiotics in two (2) or more patients within seven (7) days of the procedure

Within 24 hours of notification, the Sponsor will report the event to the DMC Chair for evaluation. The DMC Chair will review the event and decide whether to convene a meeting of the DMC.

In all cases, the DMC Chair or the DMC will be responsible for recommendations to continue the trial, continue the trial with modifications, pause the trial such that further evaluation can be conducted, or terminate the trial.

12 ADVERSE EVENTS / SERIOUS ADVERSE EVENTS

12.1 Definitions

An **adverse event (AE)** is defined as any undesirable experience occurring to a Subject during the course of the study, whether or not it is related to the test material or the study procedure. Expected adverse events are those that are listed as known risks of the liposuction or injection procedure including those described in this protocol, informed consent, and/or the Investigator's Brochure.

A **serious adverse event (SAE)** is defined as any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
- Requires or prolongs Subject hospitalization
- Results in persistent or significant disability or incapacity
- Is an important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the Subject or require intervention to prevent one of the above outcomes
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate.

An **Unanticipated Adverse Device Effect** is defined as any serious adverse effect on the health and safety or any life-threatening problem or death caused by, or associated with the Celution or Puregraft system devices, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application or any other unanticipated serious problem with the Celution or Puregraft system devices that relates to the rights, safety or welfare of subjects.

12.2 Procedures for AE Reporting

All AEs will be recorded by the investigator or designee on the appropriate electronic case report form (eCRF). Events that occur prior to the liposuction-related activities, including those that are considered serious, are to be recorded in the medical history. Events, including SAEs, which occur after liposuction-related activities are initiated on procedure day, are to be recorded on the AE eCRF. The investigator will evaluate the relationship of the adverse event to both the test material and study procedure as unrelated, unlikely, possibly, probably, or definitely related and will record the findings, including all pertinent details of the event on the eCRF.

In addition, the Investigator or designee will report any serious adverse events, including UADE, occurring during this study to the Sponsor and Medical Monitor as soon as possible, but no later than 24 hours after the Investigator first identifies the adverse event.

The Investigator will take appropriate measures to ensure the subject's well-being and document these measures on the appropriate eCRF.

All serious adverse events experienced will be monitored until the event has resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Medical Monitor, or until there is a satisfactory explanation for the changes observed.

12.3 Adverse Event Terminology

Specific adverse events of interest are described in *Appendix B, Adverse Event Terminology and Grading* (from National Cancer Institute Common Terminology Criteria for Adverse Events). When an AE of interest occurs, the Investigator will apply the terminology in Appendix B, *Adverse Event Terminology and Grading* and indicate the grading.

12.3.1 Injection Site Related Adverse Events

Injection site related adverse events are outlined in Appendix B, *Adverse Event Terminology and Grading* (i.e. from National Cancer Institute Common Terminology Criteria for Adverse Events).

13 EMERGENCY DEVIATION FROM THE PROTOCOL

In case of an emergency threatening the continued well being of the Subject, the Investigator may deviate from the protocol. The circumstances necessitating the deviation and the

intervention(s) required will be recorded on the eCRF. The Sponsor must be notified as soon as possible, but no later than 5working days after event(s) occurred.

14 REGULATORY OBLIGATIONS AND STUDY REQUIREMENTS

14.1 FDA and Institutional Review Board Approval

Study initiation will not take place until the following regulatory requirements are met:

- Food and Drug Administration (FDA) approval with accompanying approval letter.
- Local Institutional Review Board (IRB) full approval with accompanying approval letter.

14.2 Informed Consent

Written informed consent will be obtained from all Subjects prior to the initiation of any study specific procedures. No tests or procedures required in this protocol that are outside the standard practice for treating hamstring tears will be initiated prior to obtaining written informed consent. The original ICF will be filed in the Investigator Site File.

14.3 Monitoring Procedures and Data Management

14.3.1 Site Qualification

A site qualification visit will be performed to evaluate site facilities, Investigator qualifications, adequacy of staffing, and understanding of clinical and regulatory requirements.

14.3.2 Site Training

All Investigators and appropriate study staff will be required to participate in a site training (or initiation if appropriate) to provide orientation and training to the Celution System, the Puregraft System, the STYLE Trial protocol, eCRFs and other study related documents and procedures.

14.3.3 Monitoring

During the course of the study, a representative of the Sponsor will make site visits to review protocol compliance, compare eCRFs and individual subject's medical records, assess test article accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that Subject confidentiality is maintained.

Reviewing the eCRFs for completeness and clarity, and cross-checking with source documents and reviewing any discrepancies or issues with the Investigator will be required to monitor the progress of the study. Moreover, regulatory authorities (United States Food and Drug Administration) and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be

required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality.

14.3.4 Reporting Requirements

The following reports are required of the Investigator:

- eCRFs for each subject entered into the study (this includes all screen failures as well)
- Reports of any SAEs within 24 hours of becoming aware of events
- Final report at the conclusion of the study
- Progress reports to the Sponsor, clinical monitor, and IRB at regular intervals – at least yearly
- Report to the Sponsor, within 5 working days, of withdrawal of approval by the reviewing IRB
- Report to the Sponsor and IRB of any emergency changes made to the protocol to protect the life or physical wellbeing of a Subject no later than 5working days after the emergency occurred

14.3.5 Data Management

Data management will be conducted by the Sponsor or designee, and will include a data management plan and data verification guide developed according to protocol requirements.

14.4 Study Center and Investigator Requirements

To protect the rights and welfare of Subjects, the study will be conducted in conformance with the Declaration of Helsinki, the guidelines on GCPs, Code of Federal Regulations (21 CFR 11, 50, 56, 812, 814 and 820) and applicable local laws and regulations pertaining to the conduct of the study and the protection to human Subjects.

All Investigators, sub-investigators and study personnel are required to read and follow the protocol, as well as any literature that accompanies the products prior to conducting the study procedure for the first time. In addition, all Investigators will sign and date the Investigator Statement Page of this protocol. All Investigators participating in this study will be trained in the proper use of the study procedure and in the components of this protocol.

The Principal Investigator (PI) is ultimately responsible for the conduct of this study; however, he/she may designate a member of his/her staff to assist with the collection of data and completion of eCRFs. The designee(s) will be documented on an authorization form that is signed by the PI and kept in the Regulatory Binder, to be updated as necessary. Current copies of the authorization form will be forwarded to the Sponsor.

Obtaining informed consent in accordance with national policy is mandatory for Subject participation. All Subject data is kept confidential and procedures will be implemented to ensure that Subject confidentiality is not compromised.

If additional materials are used for screening and recruitment or provided to study Subjects (i.e. advertisements, recruitment materials) they must be approved by Kerastem and the Institutional Review Board at the clinical site prior to use. Documentation of the approved informed consent must be provided to Kerastem prior to study commencement at the clinical site.

After a Subject has signed the Informed Consent Form, an eCRF will be initiated. After this point, the reason(s) must be documented on the report form for any Subject who has dropped, withdraws, or for any reason cannot complete this study.

14.4.1 Study Center Requirements

Due to the nature of the STYLE Trial, centers will be considered for participation only if the meet the following minimum facility requirements:

1. Familiarity with FDA authorized IDE and/or IND Clinical Trials within the United States
2. Affiliated pharmacy or laboratory capable of performing clinical trial randomization and cell dose preparation
3. Ability to adhere to strict compliance with the STYLE clinical protocol for all study related procedure and observations.
4.

15 PUBLICATIONS

Following completion of the study, Kerastem will present the study data in a clinical study report that will be delivered to the FDA according to US regulations.

In the event the investigator wishes to present or publish any study data (partial or complete), he/she must submit the presentation / publication draft to Kerastem for review within 30 days of the planned submission or presentation.

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APPENDIX A: SCHEDULE OF PROCEDURES

	Pre-procedure Assessment	Procedure Day		Post-Operative Follow-up Week				
	Day -28 to Day-7	Day -1	Day1	1 ± 1 day	6 ± 3 days	12 ± 1 wk	24 ± 2 wks	52 ± 2 wks
Informed consent	X							
Confirm Inclusion / Exclusion criteria	X	X						
Medical history including Demographics	X	X[1]						
Physical examination	X	X	X	X	X	X	X	X
Vital signs	X	X	X[2]	X	X	X	X	X
Laboratory tests	X	X	X					
Pregnancy test[3]	X	X	X					
Injection assessment	X							
Global Photography	X				X	X	X	X
Trichogram capture	X				X	X	X	X
Investigator Hair Satisfaction Questionnaire					X	X	X	X
Subject Hair Satisfaction Questionnaire					X	X	X	X
Randomization			X					
Sterility Testing			X					
Injection Procedure			X					
Adverse Events			X	X	X	X	X	X

1. Adverse Events that occur prior to the liposuction-related activities, including those that are considered serious, are to be recorded in the medical history.
2. Vital signs will be monitored according to institutional procedures; it is suggested that vitals be monitored frequently during the fat harvest, between fat harvest and cell injection and during cell injection procedure and for at least one hour following the injection procedure
3. Women of child-bearing potential

APPENDIX B: ADVERSE EVENT TERMINOLOGY AND GRADING

(Adapted from National Cancer Institute Common Terminology Criteria for Adverse Events)

		Severity Grading				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Bruising	Localized or in a dependent area	Generalized	-	-	-
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	-	-	-
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	-	-	-
Injection site reaction/ extravasation changes	Injection site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	-	-
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
Hemorrhage/bleeding associated with surgery, intra-operative or postoperative	Hemorrhage with surgery	-	-	Requiring transfusion of 2 units non-autologous pRBCs beyond protocol specification; postoperative interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death

		Severity Grading				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Infection with normal ANC or Grade 1 or 2 Neutrophils at the site of liposuction or cell-enriched injection	Infection with normal ANC at the site of liposuction or ADRC injection	-	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
Pain at the site of liposuction or cell-enriched injection	Pain	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	-

APPENDIX C: SUMMARY OF CLINICAL WORKFLOW