STATISTICAL ANALYSIS PLAN

Efficacy and safety of non-expanded autologous mobilized CD133+ cells to treat patients with Asherman's Syndrome: Prospective, multicenter, phase I/II clinical trial.
(ENTIRE - ENdometrial TIssular REnovation)

IGX1-ENT-XS-16-01*

**The code is assigned by the study promoter*

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Efficacy and safety of non-expanded autologous mobilized CD133+ cells to treat patients with Asherman's Syndrome: Prospective, multicenter, phase I/II clinical trial.

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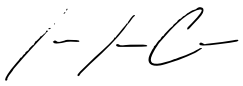
Reviewer and Approver: Signature and Date:	August 31st, 2020 
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List of Abbreviations

3D	Three Dimensions
AE	Adverse Event
AFC	Antral Follicular Count
AFS	American Fertility Society
ALT	Alanine Aminotransferase
AMH	Anti-Mullerian Hormone
ART	Assisted Reproductive Treatment
AS	Asherman Syndrome
ASRM	American Society of Reproductive Medicine
AST	Aspartate Aminotransferase
BMDSC	Bone Marrow derived Stem Cells
BST	Blood and Tissue Bank (from Banc de Sang i Teixits)
BrdU	Bromodeoxyuridine
CEIm	Research Ethics Committee with Medicines (from Comité de Ética de la Investigación con medicamentos)
CFA	Antral Follicle Count
CL	Corpus Luteum
CPSP	Peripheral Blood Stem Cells
CRA	Clinical Research Associate
CRDe	Electronic Case Report Form
DET	Double Embryo Transfer
DGP	Pre-implantation Genetic Diagnosis
DNA	Deoxyribonucleic Acid
E2	Estradiol
EA	Endometrial Atrophy
EAI	Autoimmunity Study
EB	Endometrial Biopsy
ECO	Ultrasound
ECOG	Eastern Cooperative Oncology Group
ERA	Endometrial Receptivity Analysis
ESGE	European Society of Endoscopic Gynecology
ESH	European Society of Hysteroscopy
EU	European Union
FA	Attributable Fraction
FGE	Estimated Glomerular Filtration Rate
FISH	Fluorescence In Situ Hybridization
FIV	In Vitro Fertilization
FSH	Follicle-Stimulating Hormone

G-CSF	Granulocyte Colony-Stimulating Factor
GCP	Good Clinical Practices
GNRH	Gonadotropin-Releasing Hormone
HBcAg	Hepatitis B Core Antigen
HBsAg	Hepatitis B Surface Antigen
HCG	Human Chorionic Gonadotropin
HIP/CI	Patient Information Sheet/Informed Consent
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HRT	Hormone Replacement Therapy
HSC	Hysteroscopy
HUVH	Vall d´Hebron University Hospital
ICSI	Intracytoplasmic Sperm Injection
IF	Implantation Failure
IMC	Body Mass Index
IP	Investigational Product
IR	Implantation Rate
LB	Live Born
LBR	Live Birth Rate
LE	Endometrial Fluid
LH	Luteinizing Hormone
MII	Metaphase II Oocytes
NHS	National Health System
OCE	External Cervical Os
OPR	Ongoing Pregnancy Rate
OVODON	Egg Donation
P4	Progesterone
PBS/EDTA	Phosphate-buffered saline/Ethylenediaminetetraacetic acid
PMN	Polymorphonuclear cells
PR	Pregnancy Rate
QoL	Quality of Life
RA	Attributable Risk
RAG	Serious Adverse Reaction
RAGI	Serious and Unexpected Adverse Reaction
RNA	Ribonucleic Acid
RNV	Live Newborn
RR	Relative Risk
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SET	Single Embryo Transfer
SETH	Spanish Society of Thrombosis and Haemostasis
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper Limit of Normal
VF	Final Visit of the study
VFP	Post-treatment Final Visit
VHC	Hepatitis C Virus
WOI	Window of Implantation
allo-HSCT	Allogeneic Hematopoietic Stem Cell Transplant
qPCR	Quantitative Polymerase Chain Reaction
BETA hCG	beta Chain of the Human Chorionic Gonadotropin

1. Índex

Contents

2. Introduction

2.1 Background and Rationale

Certain pathological entities, such as Asherman's Syndrome (AS) and endometrial atrophy (EA), share a common pathophysiology: the absence of functional endometrium leading to infertility. Therefore, stem cell therapies aimed at the endometrial niche with the ultimate goal of improving endometrial function may offer a promising option for treating these conditions and promoting the regeneration of pathological endometrium.

The use of CD133+ autologous bone marrow-derived stem cells (BMDSCs) has been applied in several clinical trials for patients with chronic total occlusion, myocardial infarction ischemia, hepatic fibrosis, and liver regeneration, as well as bone regeneration, demonstrating an excellent safety profile. All these findings support the use of this subtype of stem cells to treat endometrial pathologies such as AS and EA, also highlighting the potential use of stem cells to address these incurable conditions.

Recently, an open-label, uncontrolled, prospective experimental study was reported involving 18 patients aged between 30 and 45 years with refractory AS or EA (Santamaria et al., 2016). Sixteen of them completed the study, with the primary objective being to evaluate the use of CD133+ BMDSCs as a potential therapy for refractory cases of AS and EA. This study was designed as a pilot, where each patient served as their own control after failed surgical treatments and Assisted Reproductive Technologies (ART). Other studies (Nagori, Panchal, and Patel, 2011; Singh et al., 2014) have also suggested positive results in the treatment of AS patients using stem cell therapies aimed at regenerating the endometrium.

This study aims to introduce a new approach to a specific type of pathophysiology in reproductive medicine that currently lacks therapeutic options (reduced or dysfunctional stem cells in the endometrium). The goal is to regenerate endometrial tissue through the instillation of bone marrow stem cells, which are known to play a role in the homeostasis of this tissue.

The expected results would involve achieving pregnancy in patients who are unable to conceive due to issues within the endometrial cavity, characteristic of such pathophysiologies. After intra-arterial instillation of bone marrow stem cells (specifically CD133+ cells), an improvement in the uterine cavity is anticipated, resulting from endometrial regeneration.

2.2 Purpose of the Analysis

These analyses will evaluate the safety and efficacy of the Investigational Product, with the subject serving as their own control, and will be included in the clinical study report.

2.3 Purpose of the Statistical Analysis Plan

The objective of this Statistical Analysis Plan or SAP is to describe the statistical analyses that will be carried out at the end of this study. This SAP is added to the study protocol, prior to the database lock and before any analyses are conducted. The study follow-up is carried out in accordance with ICH GCP (Good Clinical Practice) guidelines. This SAP should be read in conjunction with the study protocol and the CRF.

3. Study Objective and Endpoints

3.1 Hypothesis

To regenerate the endometrium de novo through the use of autologous bone marrow stem cells, obtained by the prior mobilization and collection of Peripheral Blood Stem Cells (PBSC) via apheresis and selection of CD133+ cells, followed by transplantation of those cells in patients with moderate and/or severe Asherman's Syndrome who are planning to undergo Assisted Reproductive Technology (ART).

3.2 Objectives

3.2.1 Main Security Objective

The primary objective of this study is to evaluate the safety and tolerability of the investigational product IGX1 (CD133+ cells selected after prior mobilization and collection of peripheral blood stem cells (PBSC) from the patient) in improving post-treatment reproductive prognosis, as measured by:

Identification of the incidence, prevalence, and frequency of different adverse events that may occur throughout the study until 15 months post-treatment in the patient.
In the case of a full-term pregnancy, identification of the incidence, prevalence, and frequency of different adverse events that may occur during pregnancy, delivery, and the puerperal period.
In the case of a Live Birth (LB), identification of the incidence, prevalence, and frequency of different adverse events that may be related to the investigational product (IP) up to the first month of age.

3.2.2 Secondary Efficacy Objectives

- Proof of concept of the efficacy of the investigational product IGX1 in improving post-treatment reproductive prognosis, as measured by:

1. Live Birth Rate (LBR), Implantation Rate (IR) per transferred embryo, Pregnancy Rate (PR), and Ongoing Pregnancy Rate (OPR) per transfer performed, from embryo transfer until delivery.

2. Improvement of the hysteroscopic score based on the criteria of the different European Societies (European Society of Hysteroscopy – ESH – and European Society of Gynecological Endoscopy – ESGE) 28 days after stem cell treatment.

3. Improvement of endometrial thickness and pattern via ultrasound 28 days after stem cell treatment.

- Gestational follow-up, evaluated by the live birth rate (LBR), miscarriage rate (clinical and biochemical), and ectopic pregnancy rate from embryo transfer until delivery.
- Recovery of endometrial volume measured via 3D ultrasound 28 days after stem cell treatment.
- Analysis of endometrial vascularization through pre- and post-treatment endometrial biopsy 28 days after stem cell treatment.
- Evaluate the reappearance of menstrual episodes (if absent before treatment) or compare differences in their duration and quantity after stem cell treatment until embryo transfer, compared to pre-treatment menstrual episodes.

- Determine the cellular dose, the cut-off point for the number of CD133+ cells, beyond which it is possible to discriminate between pregnancy/no pregnancy (response variable) according to established minimum quality requirements (sterility, cell viability greater than or equal to 50%, and purity greater than or equal to 70%), and thus determine the sensitivity and specificity of the product before its use.
- Evaluate and describe the quality of life (QoL) of the participating patients using the FertiQoL International 2008 tool, in order to estimate the influence and impact of psychological issues related to infertility on various areas of daily life, before and after treatment.

3.2.3 Exploratory Objectives

- Study of the endometrial receptivity profile to detect potential alterations in the window of implantation (WOI), measured by the Endometrial Receptivity Analysis (ERA) test before and after stem cell treatment. This includes attempting to elucidate potential predisposing factors or causes that may link Asherman's Syndrome with endometrial receptivity genes.
- Study of the endometrial microbiome to establish its potential impact on Asherman's Syndrome and its relationship with the outcomes of assisted reproductive treatments, using next-generation sequencing (NGS) technologies to compare microbial profiles in endometrial fluid and biopsy samples.

- Histological study of endometrial biopsies before and after stem cell treatment to compare differences in endometrial structure and tissue regeneration mechanisms, aiming to evaluate possible mechanisms of action.

- Determination and characterization of the CD133+ cell population with new cell markers to define therapeutic cell populations by taking a small aliquot.

- A follow-up sub-study to assess macroscopic, microscopic (pathological anatomy), and genetic characteristics of placentas from newborns of pregnant women treated with IGX1, in comparison to a control group, with the aim of identifying the potential occurrence of placental problems (such as placenta accreta or percreta).

- Study of the endometrial receptivity profile to detect possible alterations in the window of implantation (WOI), measured by the Endometrial Receptivity Analysis (ERA) test before and after stem cell treatment, as well as to try to elucidate potential predisposing factors or causes that may link Asherman's Syndrome with endometrial receptivity genes.

- Study of the endometrial microbiome to establish its potential impact on Asherman's Syndrome and, therefore, its relationship with the outcomes of assisted reproductive treatments, using next-generation sequencing (NGS) technologies to compare microbial profiles from endometrial fluid and biopsy samples.

- Histological study of endometrial biopsies before and after stem cell treatment to compare differences in endometrial structure and tissue regeneration mechanisms, in order to evaluate possible mechanisms of action.

- Determination and characterization of the CD133+ cell population with new cell markers to define the therapeutic cell populations through the collection of a small aliquot.

- A follow-up sub-study to include macroscopic, microscopic (pathological anatomy), and genetic evaluation of placentas from newborns of pregnant women treated with IGX1, in comparison with a control group, to identify the potential occurrence of placental problems (such as placenta accreta or percreta).

3.3 Criteria for Assessing Variables of Interest (Endpoints)

In this section, the primary, secondary, and exploratory assessment criteria or endpoints are listed separately, along with the number and timing of evaluations/measurements taken. Section 12, Appendix A, "Study Visit Schedule" (In the protocol, Section 6.1 Study Design and Outline), describes the frequency and timing of all observations or evaluations relevant to the endpoints.

3.3.1 Primary or Safety Endpoints

Summary of all adverse events and laboratory evaluations by type, nature, incidence, and outcome overall and by the underlying disease etiology or procedure. The incidence of adverse events, serious adverse events, adverse events leading to discontinuation, adverse events leading to dose infusion delay, adverse reactions for the studied population, and deaths.

The evaluation of adverse events is conducted continuously during treatment and up to 15 months after the infusion of the investigational product (i.e., during follow-up visits).

The complete blood analysis (biochemical, hematological, hemostasis, and serological) is performed according to the protocol-planned visits at Visit 2 and Visit 4, collecting all necessary laboratory safety parameters.

3.3.2 Secondary or Efficacy Endpoints

All efficacy assessment criteria or endpoints measured in this phase I/II study are part of the secondary and exploratory objectives. The analysis populations include all exposed patients or safety population, the intention-to-treat (ITT) population, and the per-protocol (PP) population.

3.3.2.1 Morphological and Functional Changes of the Endometrium

These assessment criteria are evaluated for all patients exposed to the investigational product (IP) or within the safety population, without the requirement to proceed with the subsequent ART therapy.

All morphological criteria are measured at two time points: the first pre-treatment as a control, and the second post-treatment. During Visit 3, the pre-treatment (control) endometrial diagnosis is conducted using 2D/3D ultrasound in the luteal phase to assess the pattern, thickness, and endometrial volume, a diagnostic-surgical hysteroscopy to diagnose the degree of Asherman's Syndrome, and an ERA test. In Visit 6, 28 days after stem cell treatment, the post-treatment assessment is performed by reviewing the estradiol and progesterone regimen, 2D/3D ultrasound to evaluate endometrial thickness, pattern, and volume in the luteal phase, a diagnostic hysteroscopy, an ERA test, and an analysis of the endometrial microbiome.

Hysteroscopic Score

Improvement in the hysteroscopic score 28 days after stem cell treatment. The adhesion score or hysteroscopic score will be evaluated by the physician based on the hysteroscopy. It is assessed through hysteroscopic visualization of the uterine cavity and categorized on an ordinal scale using the ESHRE/ESGE/ASRM scale.

- Hysteroscopic score based on the criteria of the different European and American Societies (European Society of Hysteroscopy – ESH – and European Society for Gynecological Endoscopy – ESGE). See Appendix 3 of the protocol) (categorical, ordinal variable): patient evaluation at V3 and V6/Final Follow-up Visit (FFV).

Endometrial Thickness and Pattern

Improvement in Endometrial Thickness and Pattern 28 Days After Stem Cell Treatment. Endometrial thickness will be measured in millimeters using 2D/3D ultrasound. We expect to observe an improvement in endometrial thickness of at least 20% and an improvement in the regularity and endometrial pattern (which should be regular and secretory).

- Endometrial Thickness in Millimeters (Numerical Variable): Measured during Baseline Visit / V1, V3, V6 / Final Follow-up Visit (FFV), ART Visit, and Follow-up / Final Visit (FV), as well as during unscheduled visits (with more than two repeated measurements).

- Trilaminar/Diffuse Endometrial Pattern (Binary Variable): Assessed during Baseline Visit / V1, V3, V6 / FFV, ART Visit, and Follow-up / Final Visit (FV), as well as during unscheduled visits (with more than two repeated measurements).

Endometrial Volume

Recovery of Endometrial Volume Measured by 3D Ultrasound 28 Days After Stem Cell Treatment. Endometrial volume is measured in cubic centimeters using 2D/3D ultrasound. An increase of at least 25% in endometrial volume is expected after the treatment.

- Endometrial Volume in cm^3 (Numerical Variable): Measured during Baseline Visit / V1, V3, V6 / Final Follow-up Visit (FFV), ART Visit, and Follow-up / Final Visit (FV), as well as during unscheduled visits (with more than two repeated measurements).

Endometrial Vascularization

Analysis of endometrial vascularization through pre- and post-treatment endometrial biopsy 28 days after stem cell treatment. An increase in the number of vessels will be measured by digital histology or immunofluorescence using the Alpha-ASMA marker.

When immunohistochemistry will be used to detect the presence of α-SMA in endometrial tissue through pre- and post-treatment biopsies, taken 28 days after stem cell treatment, which will be associated with the presence of blood vessels. The result will be images showing the distribution of α-SMA in the tissue.

Mature Blood Vessels (Numerical Variable): Biopsy taken during Visit 3 (V3) and Visit 6 / Final Follow-up Visit (FFV) (two measurements: before and after treatment). There is a possibility of additional biopsies during unscheduled visits (with more than two repeated measurements).

3.3.2.2 Results of ART (Assisted Reproductive Technology) or Spontaneous Pregnancy

In the case of ART during the first 6 months, a visit to check the β-hCG result will be scheduled according to standard clinical practice (approximately 10-14 days post-transfer). If there is a progressing pregnancy, the following will be carried out follow-up visits during pregnancy: These will coincide with standard clinical practice, i.e., at weeks 12-14, 22-24, and 34-36.

- Implantation rate (IR): Calculated as the number of implanted embryos divided by the number of transferred embryos.
- Pregnancy rate (PR): The number of patients with a positive serum level of β-human chorionic gonadotropin (βhCG > 25 mIU/ml) per embryo transfer (ET), following ART or spontaneous pregnancy.
- Ongoing pregnancy rate (OPR): Calculated per transfer, from embryo transfer to delivery. This will consider pregnancies beyond 12 weeks of gestation, following ART or spontaneous pregnancy. If contact with the patient is lost before 12 weeks of ongoing pregnancy after ET, the case will be considered lost during follow-up and classified as “No OPR” in the analysis. If follow-up is lost after 12 weeks but before the live birth, it will be classified as a loss of follow-up with "OPR."
- Live birth rate (LBR): The number of deliveries that resulted in at least one live birth from all patients included in the study. A live birth is defined as the complete expulsion or extraction of a product of conception from a woman after 22 weeks of gestation, which, after separation, breathes or shows any other signs of life, such as a heartbeat, umbilical cord pulsation, or definite movement of voluntary muscles, regardless of whether the umbilical cord has been cut or the placenta is attached.

3.3.2.3 Gestacional follow-up

Gestational follow-up of the population with positive β-hCG after ART or spontaneous pregnancy:

- Clinical miscarriage rate (CMR): The number of spontaneous pregnancy losses where a gestational sac was previously observed, divided by the number of pregnancies.
- Biochemical pregnancy rate (BPR): The number of pregnancies diagnosed only by the detection of βhCG, without a gestational sac being visualized via vaginal ultrasound in the fifth week of pregnancy, divided by the number of pregnancies.
- Ectopic pregnancy rate (EPR): The number of pregnancies occurring outside the uterine cavity, diagnosed by ultrasound, surgical visualization, or histopathology, divided by the number of pregnancies.

3.3.2.4 Menstrual Episodes

Reappearance of menstrual episodes. The menstrual history is recorded monthly by the patient, based on the following parameters: duration, volume, and frequency.

• Duration of the menstrual episode in days (numerical variable): recorded in the calendar monthly for each menstrual cycle, both before the instillation and for six consecutive months after the cellular instillation.
• Bleeding volume in number of pads per day (numerical variable): recorded in the calendar monthly for each menstrual cycle, both before the instillation and for six consecutive months after the cellular instillation.
• Frequency of menstrual episodes in days (numerical variable): recorded in the calendar monthly for each menstrual cycle, both before the instillation and for six consecutive months after the cellular instillation.

3.3.2.5 FertiQoL International 2008 Questionnaire: Quality of Life

To evaluate the quality of life of all participants, the Fertility Quality of Life Questionnaire (FertiQol) was used. Assessments are made at the start (V1 / Baseline Visit) and at the end of the IVF cycle (VF up to month 15 (±1)).
The "FertiQoL International" questionnaire consists of two parts: the "FertiQoL International Fertility Quality of Life Questionnaire" -Core-FertiQoL- (2008) and the "FertiQoL International Optional Treatment Module" -Treatment-FertiQoL-.
The core module (Core-FertiQoL) consists of 24 questions grouped into 4 subscales, assessing quality of life in 4 areas (6 questions each):emotional: individual experiences commonly associated with fertility problems, such as envy, resentment, and depression.Mind and body: referring to physical symptoms like pain and fatigue, as well as cognitive or behavioral disorders like lack of concentration.
Relational: indicating problems in the relationship with one's partner, including sexual, communication, and cohabitation issues.
Social: measuring impact on social interactions, social inclusion, stigma, support, expectations, etc.
The optional treatment module (Treatment-FertiQoL) evaluates the quality of life related to fertility treatment itself. It consists of 10 questions and assesses the perception of treatment across two subscales treatment environment (6 questions)treatment tolerability (4 questions).
Each question is rated on a Likert scale from 0 to 4, with the higher value corresponding to a better quality of life.
Using the "FertiQoL Scoring" table, a score from 0 to 100 will be obtained for each specific aspect and subscale of quality of life and treatment. For the items and the 6 subscales, in the overall result of the two questionnaires (Core-FertiQoL and Treatment-FertiQoL), and in the result of both combined tests, the final score range is from 0 to 100. A higher score in the total FertiQoL scale or in one of the subscales

translates to a better quality of life (Boivin et al., 2011).This is a numerical variable with two repeated measurements, taken before and after treatment with PEI.

3.3.2 Exploratory Endpoints

3.3.3.1 Endometrial Receptivity Profile

The ERA test evaluates the endometrial transcriptomic profile to determine if the patient's uterus is receptive at the time of embryo transfer during an In Vitro Fertilization (IVF) process. The ERA test identifies the patient's personalized window of implantation and can guide the specialist to select the ideal time for embryo transfer, known as personalized embryo transfer. After obtaining the transcriptomic profiles from the ERA test for each patient, the status of endometrial receptivity will be estimated as:

- **Proliferative pase**
- **PREd2**: Pre-receptive day 2 (48 hours until reaching receptivity)
- **PREd1**: Pre-receptive day 1 (24 hours until reaching receptivity)
- **eR:** Early receptive (12 hours until reaching receptivity)
- **R**: Receptive (time of receptivity)
- **IR**: Late receptive (12 hours after the receptive state)
- **Post-receptive** (more than 12 hours after the receptive state)
- **NI**: Non-informative (invalid or insufficient RNA)

According to the bioinformatics predictor of the ERA test, in cases where patients show a Receptive profile or have a slightly shifted implantation window requiring 24 hours or less of additional progesterone administration (Pre-Receptive day 1), the embryo transfer should be performed in the same type of cycle and under the conditions specified in the ERA test report.

For patients showing a Non-Receptive profile, such as Post-Receptive or Pre-Receptive requiring more than 24 hours of additional progesterone administration (Pre-Receptive day 2) in the first biopsy, it is recommended to take a second biopsy according to the ERA test estimate to confirm receptivity during the shifted implantation window (estimated in less than 10% of total cases). In rare cases, a third biopsy may be necessary.

*

TE directa sin 2ª biopsia	- Receptivas (incluyendo tempranas y tardías). - Pre-Receptivas de 1 día extra de Progesterona.
2ª biopsia recomendada antes de TE	- Post-Receptivas - Pre-Receptivas de más de 1 día extra de Progesterona.

If the ERA test result is non-informative (usually due to poor amplification or poor sample quality, estimated in less than 5.5% of cases), a biopsy may be repeated to perform the test again.

3.3.3.2 Endometrial Microbiome Profile

Microbiological profiles will be diagnosed as:

- Normal microbiota: where the sample is free of pathogenic bacteria and contains more than 90% bacteria belonging to the genus Lactobacillus.
- Abnormal or pathogenic microbiota: in cases where profiles show the presence of more than 10% pathogenic or dysbiotic bacteria and less than 90% bacteria belonging to the genus Lactobacillus.
- Ultralow/dysbiotic microbiota: where the microbial profile cannot be determined due to low bacterial biomass.

3.3.3.3 Endometrial Structure

A hematoxylin-eosin stain will be performed, and the number of endometrial cells will be manually counted, with the result expressed as a percentage of total endometrial cells.

A biopsy will be taken during V3 and V6/VFP (two measurements before/after treatment). An additional biopsy may be taken during unscheduled visits.

4 Study Methods

4.1 Study Design and General Study Plan

This is a phase I-II clinical trial of advanced cell therapy, prospective, open-label, non-randomized, uncontrolled, explanatory, multicentric, and interventional, with a single-assignment group. It is aimed at patients of reproductive age diagnosed with moderate and/or severe Asherman's Syndrome (excluding mild cases) based on criteria from various European societies (ESH and ESGE) and/or ASRM scores, who plan to undergo assisted reproduction treatment with a single blastocyst embryo transfer (day 5 or 6 of development) after receiving cell therapy for endometrial regeneration. Exceptionally, double embryo transfer (DET) cases may be accepted upon medical indication.Since this is an uncontrolled trial (before-and-after study), the aim is to demonstrate the safety and evaluate the efficacy and superiority of results after the intervention in the same group of patients, with each subject acting as her own control. It is assumed that any changes at the endometrial level will be due to the stem cell treatment the patient has undergone.

4.2 Methodology Summary

The selection and evaluation period, which includes the baseline visit (Visit 1) lasting approximately 45 days, during which patients will be selected and evaluated. The second period of the study, or open treatment and regeneration period, consists of 5 visits (Visits 2 to 6), which take place approximately from day 1 to day 37. Below is a brief summary of the study activities (see Table 10, Appendix A: Study Activity Scheme):

On day 1 (baseline visit and Visit 2), preferably on a Tuesday, the Hematology Service will evaluate the patient prior to the prescription of G-CSF. Once the hematologist gives the approval, the patient will go to the Pharmacy Service to collect the medication. Subsequently, on day 4 (+1) (Friday or Saturday), the patient will start G-CSF® treatment at home following the instructions from Hematology and Pharmacy (10 µg/kg every 24 hours for 5 consecutive days via subcutaneous injection). The home treatment will continue on days 5 and 6 (+1), either Saturday and Sunday or Sunday and Monday. The patient will then return on day 7 (Visit 3), which will be a Monday or Tuesday, for evaluation and endometrial pre-treatment diagnosis (control) via hysteroscopy, ultrasound, and endometrial biopsy for the ERA test. Additionally, a sample of endometrial fluid (LE) will be collected for microbiome analysis using NGS just before the tissue is taken for the ERA test.

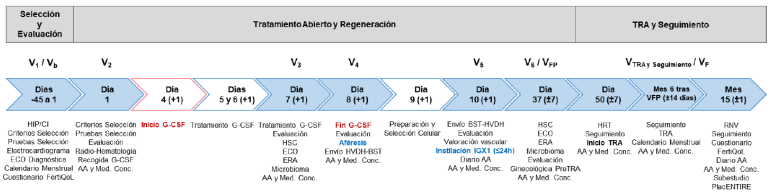
The next day, after the 5 days of G-CSF® treatment, on Visit 4 (day 8 (+1)), which will be on a Tuesday or Wednesday, the last dose of G-CSF® will be administered following a prior evaluation of the patient, and the CPSP collection will be carried out via apheresis. The CPSP samples will be sent to the processing center (central laboratory of BST) for selection and preparation prior to instillation on day 10 (Visit 5). On day 9(+1), Wednesday or Thursday, BST will conduct the processing and cell isolation to produce the investigational product IGX1. This will be sent early in the morning on day 10(+1), Thursday or Friday, for Visit 5, during which IGX1 cell instillation will be performed within the first 24 hours following the completion of PEI processing by BST, and after the patient has been previously evaluated by the medical team.

Finally, approximately 4 weeks after the cell instillation (Visit 6 or final post-treatment visit/day 37(±7)), which would correspond to approximately one menstrual cycle, a new post-treatment endometrial diagnosis will be performed to evaluate the outcome and the regeneration of the endometrial tissue. The same diagnostic tests as in Visit 3 will be conducted (i.e., ultrasound, hysteroscopy, endometrial biopsy, ERA test, and LE sampling for microbiome analysis). After the gynecological evaluation, the results will be discussed with the patient, and a joint assessment will be made before starting the ART treatment that the patient had planned to undergo, which would take place approximately 10 days after Visit 6 or the Final Post-treatment Visit (day 50(±7)).

During this visit, the patient will begin Hormone Replacement Therapy (HRT) in preparation for the start of ART, which may take place within the first 6 months post-Final Post-treatment Visit. Regardless of whether the patient and/or the medical team consider continuing with the initially established ART, a follow-up period of up to 15 months will be established from the day of the second hysteroscopy to evaluate the endometrial cavity (Visit for ART and Follow-up or Final Visit, that is, from Visit 6 to month 15). This follow-up period (with both in-person and remote visits), in patients who may or may not become pregnant following the potential embryo transfer, will include at least 5 scheduled contacts, coinciding with routine clinical practice.

Once the follow-up period is reached, both patients who complete all scheduled visits and those who withdraw before the end of this follow-up period (estimated at up to 15 months) will undergo the corresponding final visit (Final Visit) of the study. Additionally, in the case of a full-term pregnancy, a contact (in-person or remote) will be made 30 days after the Final Visit (conducted approximately in month 15 or earlier). This follow-up visit will assess the status of both the newborn and the mother.

Figura 1. Esquema global del estudio



4.1 Selection Criteria

Inclusion Criteria

1. Patients who provide written informed consent approved by the Ethics Committee for Research with Medicines (CEIm) after being properly informed of the nature of their disease and voluntarily agreeing to the treatment program, understanding the potential risks, benefits, and discomforts.
2. Patients diagnosed with moderate and/or severe Asherman's Syndrome (excluding mild cases) based on the criteria of various European Societies, who will undergo Assisted Reproduction Treatment (ART) with single embryo transfer (SET) of blastocysts (on day 5 or 6 of development) after undergoing cell therapy for endometrial regeneration.
3. Note: Exceptionally, cases of double embryo transfer (DET) may be accepted upon medical recommendation.
4. Patients who, prior to the start of the study, plan to undergo ART in a substituted cycle through Hormonal Replacement Therapy (HRT), with donated oocytes (fresh or frozen) or their own:
5. In the case of their own oocytes, at least 2 blastocysts (day 5 or 6 of development) that are euploid, analyzed through PGT, and previously vitrified will be required.
6. In the case of egg donation, the embryos can be at the blastocyst stage (fresh or previously vitrified) with or without prior PGT. If the embryos are vitrified donor embryos, a minimum of 2 vitrified embryos will be required to meet the inclusion criteria. In compliance with standard clinical practice, Preimplantation Genetic Testing (PGT) will be carried out according to what is authorized by current legislation on assisted human reproduction techniques (Law 14/2006 of May 26). The most common indications for PGT would include: Advanced Maternal Age (Age ≥ 36 years), Recurrent Implantation Failures, Recurrent Miscarriages, or Chromosomal abnormalities in one or both partners as well as sperm FISH abnormalities or other medically indicated reasons.
7. Women of reproductive age between 18 and 44 years old (inclusive).
8. BMI: 18–30 kg/m² (inclusive).
9. Adequate liver and kidney function, defined as:
10. Total bilirubin < 1.5x Upper Limit of Normal (ULN)
11. AST and ALT < 2.5x ULN, and

12. Serum creatinine < 1.0 mg/dl; if serum creatinine is > 1.0 mg/dl, then the estimated glomerular filtration rate (eGFR) should be > 60 ml/min/1.73 m².
13. Absence of severe cardiac pathology.
14. Negative blood pregnancy test.
15. ECOG score = 0-1.
16. Negative serology for HIV, HCV, HBSAg, HBcAg, and Syphilis (within the last 30 days).Estudio de coagulación normal.
17. Adequate peripheral venous access. In its absence, the investigator will assess the possibility of implanting a central venous catheter.
18. Absence of severe psychiatric disorders.
19. Patient's ability to adhere to and properly follow the study procedures and assessments, meaning patients capable of understanding and complying with the parameters as outlined in the protocol.

Exclusion Criteria

1. Patient refusal of central venous catheter implantation proposed by the investigator in case of absence of peripheral venous access.
2. Patients allergic to iodinated contrast agents.
3. Patients in whom, after the apheresis and selection process, an optimal investigational product ready for infusion has not been obtained, meeting any of the following minimum quality requirements:
   - Minimum dose to be infused lower than $30x10^6$ CD133+ cells.
   - (Note: If the investigational product meets the rest of the quality requirements for infusion, the patient may receive the IGX1 treatment even if the dose is lower than the indicated minimum. The results of this patient will not be included in the per-protocol population, but may be included in other population groups).
   - Cell viability lower than 50%.
   - Purity lower than 70%.
   - Lack of sterility.
4. Patients who have participated in another clinical trial or received investigational treatment within the last 30 days, unless expressly approved by the sponsor.
5. Presence of serious or uncontrolled bacterial, fungal, or viral infections that, in the opinion of the principal investigator, may interfere with the patient's participation in the study or the evaluation of study results.
6. Any illness or medical condition that is unstable or may endanger the patient's safety and their adherence to the study.

4.2 Trial Phase

Phase I/II.

4.3 Randomization and Blinding

Non-randomized study, it is a single-assignment group study. Since this is a non-randomized study, all patients will be assigned to the same treatment group, and no blinding process will be applied. Therefore, it is not necessary to assign a randomization number or code. All parties are aware of the treatment the participants are receiving.

4.4 Study Population

Patients aged 18 to 44 years with a diagnosis of moderate and/or severe Asherman's Syndrome based on the criteria of various European Societies (ESH and ESGE) who are undergoing ART with their own or donated oocytes and single embryo transfer (SET) of a frozen embryo at day 5/6 of development (exceptionally, a transfer of two embryos may be performed if medically indicated). These patients must have normal liver and kidney function, as well as no serological infections, and no severe cardiac, coagulation, or psychiatric disorders.

4.5 Study Variables

Primary Variables

Fort he primary objective:

- Adverse events (list) for each medical review/visit from IGX1 instillation until month 1 of the newborn (if applicable).
- Time elapsed between IGX1 instillation and the occurrence of adverse event(s) (in days).
- Hospitalization due to adverse event: YES/NO.
- Treatment required for adverse event (list).
- Each of the control lab tests performed during visits (quantitative variables).
- Apgar score (categorical variable).
- Adverse events in the newborn (list).

For the secondary objectives:

- Pregnancy: YES/NO, categorical variable
- Implantation: YES/NO, categorical variable
- Ongoing pregnancy: YES/NO, categorical variable
- Live Birth (LB): YES/NO, categorical variable
- Hysteroscopic score according to ESH/ESGE (numerical variable) before and after treatment
- Endometrial thickness in mm at each visit (numerical variable) before and after treatment, and at each visit
- ~~Endometrial pattern (trilaminar/diffuse), categorical variable before and after treatment, and at each visit~~
- Pregnancy outcome (categorical list: ongoing pregnancy, clinical miscarriage, biochemical pregnancy, ectopic pregnancy)
- Endometrial volume measurement via 3D ultrasound before and after treatment (numerical variable)

- Endometrial vascularization analysis measured by digital histology or immunohistochemistry with the presence of α-SMA expression before and after treatment
- Frequency of menstrual episodes in days (numerical variable) before and during 6 consecutive months after treatment, if applicable (if pregnancy occurs earlier, this will not be conducted)
- Duration of menstrual episodes (numerical variable) before and during 6 consecutive months after cell instillation
- Number of pads per day before and after treatment (numerical variable) before and during 6 consecutive months
- Number of CD133+ cells, explanatory variable (quantitative)
- Quality of life evolution before and after treatment (quantitative and qualitative variables described in Appendix 20.4 of the protocol)

For the exploratory objectives:

Endometrial receptivity diagnosed with ERA as Receptive/Non-Receptive (categorical variable) before and after treatment. Among Non-Receptive patients, the following possibilities may be found:

- F: Proliferative phase
- PREd2: Pre-Receptive day 2 (48 hours to reach receptivity)
- PREd1: Pre-Receptive day 1 (24 hours to reach receptivity)
- PREt: Late Pre-Receptive (12 hours to reach receptivity)
- R: Receptive (moment of receptivity)
- eT: Early Post-Receptive (12 hours after reaching receptivity)
- T: Post-Receptive (more than 12 hours after reaching receptivity)

- A variable for each gene found in the ERA test from the endometrial biopsy and endometrial fluid before and after treatment.
- A variable for each microorganism found in the biopsy and endometrial fluid before and after treatment..
- Microbiome found in biopsy and endometrial fluid (LD/NLD) before and after treatment: Presence of bacterial microbiome; the identified bacteria will be classified into two groups:

- Group 1 (LD): Lactobacillus-dominant microbiome (>90% Lactobacillus spp.), composed of various species of the Lactobacillus genus: L. crispatus, L. gasseri, L. iners, L. jensenii, among others.
- Group 2 (NLD): Non-Lactobacillus-dominant microbiome (<90% Lactobacillus spp. with 10% dysbiotic bacteria), composed of species that alter endometrial physiological conditions, thus reducing the prevalence of Lactobacillus.
    - Results of the histological study of the endometrial biopsies before and after treatment (categorical variable: normal/abnormal).
    - Surface markers VEGFR (Vascular Endothelial Growth Factor Receptor), CD38+, others.

Control Variables: These will be used to control the primary variables of the study

- Number of CD133+ cells injected (numerical variable) greater than 30 million cells.
- Cell viability percentage (numerical variable) equal to or greater than 50%.
- Cell purity percentage (numerical variable) equal to or greater than 70%.
- Each baseline blood analysis (before treatment), quantitative variables.
- Details of HRT for the biopsy collection for basal ERA and post-treatment ERA: Days of estradiol, concentration of progesterone (P4) on the day of P4 supplementation initiation, time of P4 initiation, time of biopsy collection (numerical variables).
- Day of sample collection (basal and post-treatment biopsy), categorical variable in relation to the day of progesterone administration (P+4, P+5, P+6, P+7).

Descriptive Variables: Used to assess the homogeneity of the population and avoid potential biases by analyzing their distribution in each study group, or to identify factors that may affect them:

- Age (numerical variable from 18 to 44)
- Body Mass Index (BMI), numerical variable from 18 to 30
- Ethnicity/Race (categorical variable)
- Obstetric history: numerical variables for previous obstetric history: pregnancies, deliveries, cesarean sections, previous miscarriages, curettage.
- Indication for ART (list), categorical variable.
- Number of previous implantation failures (IF), numerical variable.
- Baseline FSH, numerical variable.
- Baseline AMH, numerical variable.
- Sperm concentration, numerical variable.
- Type of treatment (IVF/ICSI, egg donation), categorical variable.
- Cycle type (vitrified/fresh oocytes), categorical variable.
- Details of HRT for the biopsy collection for ERA: Days of estradiol, progesterone (P4) concentration on the day of P4 supplementation initiation, time of P4 initiation, time of biopsy collection, numerical variables.
- Day of sample collection (biopsy), categorical variable in relation to the day of progesterone administration (P+4, P+5, P+6, P+7).
- Ovarian stimulation data (type of stimulation – long or short –, days of stimulation, estradiol (E2) levels on the day of hCG, numerical variables. Dosage of follicle-stimulating hormones (FSH, LH, HMG).
- Antral Follicle Count (AFC), numerical variable.
- Number of metaphase II (MII) oocytes, numerical variable.
- Number of fertilized oocytes (to determine fertilization rate), numerical variable.
- Details of HRT for embryo transfer: Days of estradiol, progesterone (P4) concentration on the day of P4 supplementation initiation, time of P4 initiation, time of embryo transfer, numerical variables.
- Day of transfer (5/6), categorical variable.
- Number of embryos transferred, numerical variable.
- Embryo quality based on morphology of transferred embryos, categorical variable (A, B, C, D).

- Preimplantation Genetic Diagnosis (PGD) YES/NO, categorical variable.
- Number of vitrified embryos, numerical variable.
- Number of implanted sacs, numerical variable.
- Gestational age (weeks), numerical variable.
- Birth weight (kilograms), numerical variable.
- Newborn height (centimeters), numerical variable.
- Obstetric complications, categorical variable.
- Delivery complications, categorical variable.

4.7.1 Transformations and Derived Variables

The reported age in years is used; if not available, the age in years is calculated using the date of birth and the date of informed consent.
The following conversion units are applied unless otherwise specified:

Months = Days / 30.4375
Years = Days / 365.25
The values of baseline characteristics in all analyses are the most recent reported values before the administration of the investigational product (PEI).

No data transformations are planned for the primary and secondary endpoints, except for the FertiQoL scale:

Transformation of FertiQoL scores: The total and subscale FertiQoL scores are calculated and transformed into scaled scores to achieve a range of 0 to 100, facilitating comparisons across scales. Items are reverse-scored when necessary, where some items within the same group have an inverse direction compared to others. All items are summed and multiplied by 25/k, where k is the number of items in the desired subscale or the total scale.
No other transformations are expected, and there are no planned quantitative variables that would require further transformation for data processing. If the need arises during the analysis, for instance, in a model adjusted for covariates, it will be addressed with appropriate transformations, such as logarithmic, scaling, centering, or standardizing the variables.

Measurement and Calculation of Clinical Outcomes

The implantation rate is defined as the proportion of gestational sacs observed via vaginal ultrasound in week 6, over the number of embryos transferred. The clinical pregnancy rate per transfer is defined as the percentage of pregnant patients relative to the total number of transfers performed. Implantation and ongoing pregnancy are considered for pregnancies beyond 12 weeks of gestation. Clinical pregnancy rates, biochemical pregnancy, miscarriage, ectopic pregnancy, and obstetric complications are calculated based on the number of embryo transfers per cycle. Calculations for reproductive outcome rates and ART rates will be made based on the

number of transfers performed, providing rates per transfer for the per-protocol population; they will be calculated per patient in the case of ITT or safety analysis.

5 Sample size

A total of 22 patients will be included.

Our hypothesis is that stem cell transplantation into the uterine cavity improves the live birth rate (LBR) as the primary dependent variable and endometrial thickness as the secondary dependent variable.

The study will be conducted using a historical control group, which may consist of the same patient who underwent ART before treatment or historical patients with similar clinical characteristics (a "Before and After" matched cohort study).

We assume that all patients will undergo a single embryo transfer (SET) on day 5/6 of development.

IMPROVEMENT IN LIVE BIRTH RATE

Our hypothesis is that the improvement would result in an increase from 0% in the control group to 28% in the treatment group (which is the average live birth rate (LBR) reported in ART (European IVF-Monitoring Consortium (EIM) et al., Hum Reprod 2016). It should be noted that this rate is calculated based on the total number of cycles performed (embryo transfers).

Calculations for the LBR as a binary variable (the sample size will refer to the number of embryos transferred).

[Endpoint]	
Test significance level, a	0.05
1 or 2 sided test	1
Proportion difference, m_1 - m_2	0-28%
Power (%)	80
n per group	18
dropouts	20%
n per group considering dropouts	22

To determine how many patients correspond to the 22 ET (embryo transfers), we calculate that 50% will need #1 ET = 11 patients. Of the remaining 11 (who will need a second ET), we expect 70% will become pregnant = 7 patients. These calculations assume that all patients will have at least 2 embryos and that single embryo transfers (SET) will be performed.

Therefore, we would need a total of 18 patients in the study per protocol (with ET performed), as we expect them to become pregnant after 2 ETs.

Thus, the number of patients to be treated per protocol would be 18.

To calculate the total sample size by intention-to-treat (total number of patients starting the study) who may not reach the ET phase, we must account for potential losses due to various reasons before reaching the ART phase (dropout, loss of information, complications with G-CSF® treatment, apheresis, or IGX1 instillation, etc.).

Given that this is a small and highly controlled population, and expectations for treatment are high, we estimate a 20% loss. Therefore, the number of patients by intention-to-treat would be 18 + 3.6 = 22 patients in total.

6 General Considerations

6.1 Timing of the Analysis

This trial is not designed to allow for early stopping to demonstrate favorable efficacy results.

The final analysis will take place after the last patient recruited in the trial has completed treatment with the investigational product (PEI) and the follow-up period up to the final study visit (15 months after the PEI infusion), with or without completing ART treatment. The final analysis will be performed on a copy of the data after the database is locked, following the completion and approval of this SAP document.

6.2 Analysis Populations

6.2.1 Set of Recruited Patients

All subjects screened who sign the Informed Consent (IC), provide demographic measurements and/or other baseline screening measurements, and receive a subject identification code, including any admission errors, will be included regardless of any future withdrawal from treatment or protocol deviations, with or without apheresis performed.

6.2.2 Intention-to-Treat (ITT) Population

All patients recruited in the study, including admission errors, regardless of any future withdrawal from treatment or protocol deviation, who initiate treatment with G-CSF, even if they do not undergo PEI instillation.

Descriptive tables of demographic, clinical, and baseline characteristics, as well as patient lists, will be produced for the population group.

6.2.3 Exposed Population or Safety Population

The safety and efficacy population is the exposed set that includes all patients who received any study drug, whether or not embryo transfer was performed.

Therefore, the safety population will be identical to the ITT population if all recruited subjects receive pre-treatment with G-CSF and the PEI treatment.

The safety population will be used to present safety summaries and efficacy summaries. It is the primary efficacy and safety population.

Tables of clinical and baseline demographic characteristics, as well as subject listings, will be produced for the ITT and Safety populations. All safety and efficacy analyses will be performed using the safety population and the ITT population.

6.2.4 Protocol Population (PP)

All patients recruited in the study, exposed to the PEI, who:

- Meet all selection criteria.
- Receive the drug correctly: the assigned PEI, within the estimated time frame, according to the protocol and the manufacturer's instructions (section 8 of the protocol).
- Complete all phases following the protocol until the end, including embryo transfer.
- Have not experienced any major protocol deviation (section 6.3) during the study period, and have not been lost to follow-up or discontinued from the study.

6.3 Covariates, Confounding, Factors, and Effect modifiers

The following covariates, considered potential confounding factors, may be included in exploratory regression analyses of efficacy endpoints. Interaction effects will be considered when possible.

At the microbiome study level, ethnicity is a potential confounding factor to be taken into account.
Microbiome results may be affected by antibiotic use, protocol deviations in sample handling procedures, contamination, or small sample sizes. Microbiome results would only be considered valid within the first three months.

Possible confounding factors and variables that may affect the analysis at the reproductive outcome level and should be considered include:

- Woman's age and BMI
- Antibiotic or probiotic intake
- Number of previous implantation failures
- Baseline FSH, as a marker to assess ovarian reserve, helps predict the ovarian response to stimulation and decide the best stimulation protocol for patients undergoing IVF treatment, along with baseline AMH and AFC (antral follicle count), which provide lower variability and greater diagnostic reliability.
- Semen concentration
- Origin of the oocyte
- Embryo analyzed by PGS
- Ovulatory trigger medication
- Day/Stage/Quality of embryonic development at the time of transfer
- Number of embryos transferred
- Days on progesterone, dosage
- Days on estradiol, dosage

There may be residual confounding factors in our dataset that are not measured among those already mentioned. The measured variables reflect current clinical practice.
It is advisable to consider these variables when estimating whether there is an improvement in pregnancy/live birth rates, as they could mask, overestimate, or underestimate the effect of these outcomes.
A multivariate logistic regression analysis may be performed on reproductive outcomes with LB or OGP (live birth or ongoing pregnancy) as the dependent variable. However, the size of our trial is limited to controlling for all potential confounding effects using regression models with sufficient statistical power to infer reproductive outcomes through multivariate models.

6.4 Subgroups

As exploratory analyses, subgroup analyses may be considered for selected summaries. The subgroups may include, but are not limited to, the following:

- PEI dose based on the number of CD133+ cells infused (≥30 vs. <30),
- Pregnant vs. Non-pregnant,
- Live birth (LB) vs. No LB,
- Depending on whether they have a displaced endometrial profile (Yes vs. No).

6.5 Missing data

We do not expect to have missing values for the endpoint variables. No data imputation techniques are planned for missing endpoints, except for the dates of adverse events (Appendix A). For adverse events, the absence of confirmation during a visit will also be considered as the non-occurrence or continuation of the adverse event at that visit.

In the case of missing data for any endpoint or outcome in the analysis, a complete-case analysis will be applied. Excluding incomplete cases with known outcomes reduces statistical efficiency and introduces bias in estimating treatment effectiveness.

The number of subjects included in each analysis will be reported so that the potential impact of missing data can be evaluated. Information unavailable for analysis due to the withdrawal of informed consent for the use of data is not considered missing and is therefore not included in the estimation of the percentage lost.

6.6 Interim Analysis (Interim)

The data obtained in this study will be reviewed by an Independent Data Monitoring Committee (IDMC). This committee will review the accumulated data after 11 patients have entered the study and have been evaluated 30 days after treatment with IGX1. During this review, the IDMC will monitor all study data obtained, paying special attention to everything related to the safety and tolerability of the investigational product IGX1. The quality of the recorded data, all adverse events reported to date, and the progress of the study in relation to the initially proposed study objectives will be assessed. This committee may make recommendations to the sponsor regarding the continuation, early termination, modification, or discontinuation of the study. The committee's recommendations will also be considered in the design of future related studies.

No statistical penalties, stopping rules, or p-value adjustments will be applied; the interim analysis will not lead to changes in the conduct of the study (e.g., sample size re-estimation or early stopping due to demonstration of efficacy).

The interim analysis is descriptive in nature. General safety results and other secondary and exploratory endpoints will be provided, depending on availability. Tables will be produced for the study as a whole, not by subgroups. Summary tables and listings will be produced in accordance with section 7.

Considerations, summary tables, and provisional data analyses to be conducted during the study:

- This report will be generated after 11 patients have entered the study and have been evaluated 30 days after treatment with IGX1. The total number of patients considered at the time of the interim will be reported.
- Due to the characteristics of the PEI, this study does not have a stopping rule for excessive mortality.
- A summary of descriptive statistics of demographic and baseline characteristics (7.3) of the patients considered in this interim will be provided, as well as the administration of treatment (7.4) and concomitant medications (7.5).
- A summary of enrollment status (7.2.1) and patient disposition (7.2) will be provided.

Security

A general descriptive summary for the primary safety objective (9.1 and subsections). Statistics, number (%), of local reactions, systemic events, abnormal hematology and laboratory parameters, adverse events (AEs), and serious adverse events (SAEs) after the PEI dose for patients available to date.
A summary table of patients who developed any type of adverse reaction (AR), AE, and SAE by severity grade will be created. This report will include at least the first 11 patients with all available safety data at the time.

In the AE tables (section 14, List of Tables and Figures, "Table V"), the following will be considered:

N: number of subjects in the group / total sample. This value is the denominator for percentage calculations.
n: number of subjects reporting at least 1 occurrence of the specified adverse event category.
For "any event", n: the number of subjects reporting at least 1 occurrence of any adverse event.
Related: assessed by the investigator as related to the investigational product.
A bar chart will be used to represent the percentage by intensity grade of local reactions and systemic events (x-axis).

Secondary efficacy objectives

The post-treatment endometrial diagnosis will be summarized descriptively. An additional informal interim analysis will summarize the data collected in Visit 6/Final Post-Treatment Visit (VFP), addressing the secondary

objectives, where the potential reconstitution of the new endometrium, the evolution of the uterine pattern, and its endometrial receptivity will be evaluated (9.2, 9.3, and subsections). A descriptive list by patient and a general summary for the medical assessment of potential endometrial evolution and regeneration will be provided, which includes: review of the estradiol and progesterone regimen, endometrial thickness, endometrial pattern and volume in the luteal phase, hysteroscopic diagnosis grade, ERA test, and endometrial microbiome analysis (in biopsy and fluid); medical indication for continuation with ART, as well as potential reproductive outcomes.

6.7 Multicentre Study

Despite the multicenter nature of the study, we anticipate that no single center will accumulate a sufficient number of patients to allow for center-specific analysis.

6.8 Multiplicity

There are no planned multiple comparisons or multiplicity issues for the primary objective. An Alpha adjustment is not necessary in this phase I/II study.

The analyses of secondary and exploratory endpoints will be conducted for hypothesis generation, and no p-value adjustment will be required.

7 Study data summary

All data will be presented for each patient and summarized by population and/or subgroup. In general, all data will be listed, ordered by subject, and a total column will be included to summarize all subjects. Where applicable, data will be summarized by visit and/or period.

Variables will be described for the populations (ITT, Safety, and Per Protocol) and/or subgroups. The total population size relevant to each table/subgroup will be noted, and the number of available and unavailable data points will be presented in each case.

All continuous variables will be summarized using the following descriptive statistics: n (sample size), mean, standard deviation, median, maximum, and minimum. Results will be presented as mean ± SD for normally distributed data or as median and range for skewed data, along with 95% confidence intervals (CI).

The number, frequency, and percentages of observed levels will be reported for all categorical measures, using the total number of observations in the population or subgroup as the denominator unless otherwise indicated. Percentages will be rounded to two decimal places and may therefore not always sum exactly to 100%.

7.1 Protocol Deviations

Major protocol deviations (PD) are defined according to ICH E3 as important PDs, those that represent a divergence from the protocol that could have a significant effect on the integrity of the study data, related to the inclusion or exclusion criteria of the study, trial conduct, investigational product, subject management, or evaluation, and that may jeopardize the safety or rights of trial participants or the scientific value of the trial.

All PDs will be evaluated and classified according to ICH into the following categories:

- The patient does not meet the inclusion/exclusion criteria.
- The patient develops, in the investigator's judgment, a condition during the study that would lead to withdrawal, but is not adequately excluded during the process.
- Disease or underlying medical conditions that may influence the endometrial or reproductive response, or jeopardize the patient's safety in the study and/or data integrity.
- The patient takes concomitant medications prohibited by the protocol or that may affect the final outcomes of the study.
- The patient takes the investigational product and/or adjunctive medication incorrectly or under inappropriate conditions, which, in the investigator's judgment, justifies the patient's permanent withdrawal from the study.
- The correct investigational product and/or adjunctive medication is not administered.
- Administration of the investigational product and/or adjunctive medication is not in accordance with the protocol.
- Key procedures not performed or performed out of time, which, in the investigator's judgment, justify the patient's withdrawal.
- Informed consent not obtained or improperly obtained in accordance with ICH-GCP.
- Compliance with the scheduled visits.
- Initiation and full administration of G-CSF treatment.
- Hysteroscopy and diagnostic ultrasound.
- Apheresis.
- PEI instillation.
- Control tests after PEI infusion.
- Control hysteroscopy and ultrasound.
- Assisted reproductive treatment.
- Repetition of minor deviations.
- Loss to follow-up.
- Failure to obtain and record mandatory variables.

Early withdrawal from the trial due to withdrawal of consent or an SAE (including death) is not considered a PD. Protocol deviations will lead to the exclusion of the subject or part of the subject's data from at least one analysis set (Per Protocol).

A list of patients with protocol deviations will be presented. The number and percentage of patients with protocol deviations will be summarized for the entire population. Patients included in the ITT analysis set will be used as the denominator to calculate percentages. No formal statistical tests will be conducted in this section.

7.2 Patient Disposition

A tabulation of the disposition of study patients by the total for each part of the study will be provided for all enrolled patients. The number and percentage of patients who signed informed consent and are part of each population or analysis set will be summarized. The number of patients recruited in each country and each center, follow-up time, and subsequent treatment information will also be summarized. Follow-up time and subsequent treatment information will be summarized.

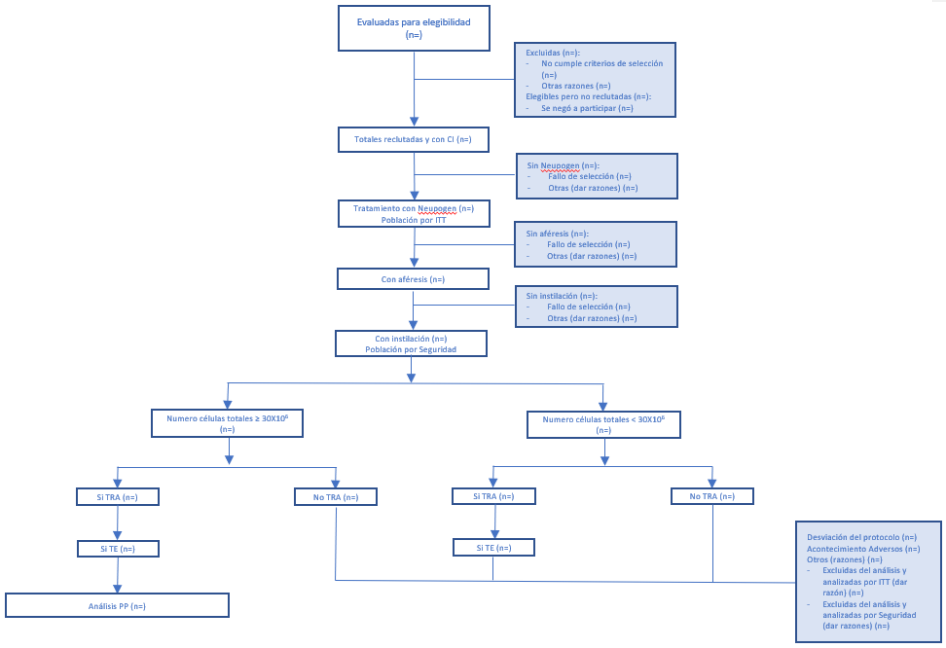
The following categories regarding patient disposition will be included in the description:

- The number (%) of patients screened and selected.
- The number (%) of patients who signed consent but were not treated.
- The number (%) of patients who completed treatment.
- The number (%) of patients who dropped out/withdrew during treatment: between the start of G-CSF and the start of PEI.
- The number (%) of patients who dropped out/withdrew from the study after completing treatment.
- The number (%) of patients who completed the follow-up period.
- The number (%) of patients in the ITT population.
- The number (%) of patients in the Safety population.
- The number (%) of patients in the Per Protocol population.

The reasons for screening failure, dropout or withdrawal from treatment, and study discontinuation, in addition to protocol deviations or loss to follow-up, will be summarized.

Patient information will be included in a CONSORT flow diagram to show the progress of participants, the number of patients, and the reasons for discontinuation throughout the study.

Disposition will be listed by patient for all recruited patients.



For the primary safety objective, enrollment will be summarized using all enrolled patients corresponding to the Safety population, as well as ITT and Per Protocol populations.
With the overall recruitment graph, and for each objective, an enrollment summary will be provided, including:

- Number of patients recruited, whether they entered treatment or not,
- Reason for not entering treatment.

The following discontinuation summary will be provided:

- Number of patients who discontinued treatment,
- Reason for discontinuing treatment,
- Number of subjects who discontinued the study,
- Reason for discontinuing the study.

7.2.1 Screening data

If available and requested, the following enrollment summaries may be presented for all screened patients: the number of recruitment days, the number of patients screened, the number of patients recruited, the number of patients recruited per day, the number of screened but not recruited patients, and the reason for non-recruitment. This summary would be provided globally and by study center.

7.3 Descriptive Statistics of Baseline Demographic and Clinical Characteristics of Patients

For all baseline demographic and clinical characteristics, as well as efficacy outcomes, the data will be presented for each patient and summarized by population and by treatment group according to the number of cells injected (≥30 or <30 million). Summary statistics will be produced in accordance with section 7.

The following characteristics will be presented per patient in table format (section 14, List of Tables and Figures, "Table I"): age, preoperative menstrual history, etiology of atrophy, number of previous attempts, number of reparative surgical hysteroscopies, obstetric history, etiology of atrophy, and previous pathologies.

The Safety, ITT, and Per Protocol populations will be used.

7.4 Treatment Administration

Patient participation will be summarized according to the Safety, ITT, and PP populations. The number (%) of patients who received the study treatment without interruption will be described, and for the ITT population, patients with treatment interruption (patients who received G-CSF without apheresis, and patients who underwent apheresis but did not receive PEI infusion) will be detailed, along with the reasons for treatment interruption.

The study medication dosage, infusion details, dose modification, and PEI batch number will be listed. A descriptive summary of the key PEI variables for the population set will be provided. Summary statistics will be produced in accordance with section 7.

The administration of IGX1 treatment per patient will be described in a table format (14 List of Tables and Figures, "Table II"): the total number of CD133+ cells (in millions), the number of doses per patient (1 or 2 doses depending on mobilization, at a single infusion time), cell viability (in %, ≥50%), cell purity (in %, ≥70%), and IGX1 dose (in ml).

The Safety, ITT, and Per Protocol populations will be used.

7.5 Prior and Concomitant Medication

Prior and concomitant medications taken or administered to a subject will be recorded in the CRF. If a subject confirms during the medical history registration that they are currently taking prescribed medications regularly, these must be documented in the CRF. After the baseline visit, any medication or therapy taken or administered to the subject during the course of the study must be recorded in the CRF. If the medication is taken to treat an adverse event (AE), the event must be recorded on the corresponding CRF page.

Concomitant medications are recorded from the start of G-CSF on day 4(+1) until the Final Study Visit at month 15(±1).

Prior medications are defined as medications that started and ended before the start of treatment at Visit 2 with G-CSF. Any prior medication taken within the previous 30 days must be recorded. Medications with a stop date before the G-CSF administration at Visit 2 will be considered prior medications. If the stop date is unknown or incomplete and the medications cannot be considered discontinued before administration, they will be considered concomitant medications.

Concomitant medications will be listed per patient, including the generic name, therapeutic group, pathology, number of reported medications, active ingredient, number of reports, and route of administration.

A summary of concomitant medication received for the treatment of any selected AE among subjects experiencing at least one AE will be provided separately for each category of selected AEs for the following specific events (14 List of Tables and Figures, “Table III”):

- Any severity and intensity AE
- Treatment-related AEs
- Serious AEs (SAEs)
- Concomitant medication received, classified by anatomical, therapeutic, and chemical class (ATC classification) and generic name
- Number of subjects who received medication
- Total duration of medication (in days, descriptive statistics)

Summary statistics will be produced in accordance with section 7. For the PP, ITT, and Safety populations, the number (%) of patients reporting the use of any prior medication will be summarized.

7.6 Medical History

Physicians/investigators must document all significant medical conditions that the subject has experienced in the past. Any medical condition present at the time the informed consent is granted should be considered concomitant. A condition that occurs or is first detected on or after the day of the initial visit and/or the worsening of a concomitant condition on or after the day of the initial visit will be documented as an AE in the CRF.

Medical history will be listed per patient by organ system classification, MedDRA, and/or preferred term.

Summary statistics for general medical history and pre-treatment events will be produced in accordance with section 7 for the ITT and Safety populations. A table will summarize (14 List of Tables and Figures, "Table IV") the number (%) of subjects reporting one or more conditions for their past medical history and the number (%) of subjects reporting each condition.

8 Statistical Methods and Considerations

There are no formal pre-specified statistical hypotheses for the primary safety objective. The minimum effective dose and the maximum safe dose are still unknown.

Any analysis outside of this plan or the protocol will be considered exploratory and will be documented in the Clinical Study Report (CSR) as a post hoc analysis or as a change to the planned analysis. If any of the proposed statistical methods prove inadequate during the final analysis, more appropriate methods will be used, and changes will be documented in the Clinical Study Report (CSR), including justification for their use. These may include data transformation (e.g., to a logarithmic scale) to meet model assumptions, such as normally distributed residuals with constant variance, or the application of other non-parametric technique.

8.1 Statistical Significance and Confidence Intervals

All hypothesis tests will be performed at a 5% significance level (two-sided) unless otherwise specified.
P-values will be rounded to three decimal places. P-values less than 0.001 will be reported as <0.001 in the tables. P-values greater than 0.999 will be reported as >0.999. Results will be presented with their values and a 95% confidence interval.

8.2 Statistical Assumptions

A normal distribution of the data cannot be assumed given the sample size used, so normality tests will be required. The Shapiro-Wilk test will be used to confirm the normal distribution of quantitative variables, and the Levene test and graphical methods will be used to assess the homogeneity of variances. Statistical assumptions will be checked graphically using distribution curves, histograms, box plots, QQ plots, and descriptive statistics.
All assumptions for regression models will be evaluated by visualizing residual plots.

8.3 Statistical Evaluation

For categorical variables, we will calculate percentages and ratios, as well as counts. Results for continuous variables will be presented as mean ± SD. Differences between groups for continuous variables will be evaluated using the Mann-Whitney U test for independent samples and the Wilcoxon test for related samples, or the Student's t-test if the necessary assumptions are met. For comparisons of more than two groups, the Kruskal-Wallis non-parametric test will be used for independent samples, or the Friedman test for repeated measures, or ANOVA if the necessary assumptions are met.

For differences between independent groups for categorical variables, the Chi-square test or Fisher's exact test will be used if any cell in the contingency table has a value less than 5. To compare the observed proportion of a dichotomous variable in two dependent or related samples (before-after treatment), the McNemar test will be used, or the exact McNemar test with a binomial distribution if b + c in the 2 × 2 table is small (b+c<25). If there are more than two categories for two dependent samples, the McNemar-Bowker test will be used.

P-values and confidence intervals (CIs) from the statistical tests performed will be presented, along with summary tables containing the coefficients, CIs, p-values, and estimated values from the possible models considered. The analyses and statistical tests will serve hypothesis-generating purposes.

9 Data analysis

The safety population is identical to the ITT population if all recruited subjects receive the study treatment. Therefore, descriptive data will be presented, and all analyses will be performed for the ITT population only if any of the randomized subjects do not receive treatment, in addition to the Per Protocol population.
Summary tables will be produced in accordance with section 7 for all outcomes or endpoints and variables of interest; data will be presented for each patient, summarized by population and/or subgroup.

9.1 Primary Analysis: Safety

There is no formal statement of null and alternative hypotheses; the nature of the primary analysis is descriptive.
Safety will be evaluated through a summary of adverse events and compliance with the study treatment. Summary tables will be produced in accordance with section 7 with safety data and will be summarized for the safety population and per protocol.

9.1.1 Adverse Events (AEs)

A treatment-emergent adverse event (TEAE) is defined as a new adverse event (AE) or a worsening of a pre-existing AE that occurs after the first infusion of the investigational product (IP).

Subcategories of Adverse Events (AEs):

- Serious Adverse Events (SAEs): An AE that is classified as serious. Any missing serious criteria will be clarified by the Clinical Research Associate (CRA) and must be completed, or the event will be considered of the highest severity in the absence of information.
- Treatment-Related Adverse Events: Any AE for which the relationship to the study drug is recorded as related to the study treatment.

Event Distinct from AE:

Infusion-Related Adverse Reactions (ARs): Defined as any event classified as an adverse reaction by the investigator. The incidence of ARs will be summarized by preferred term and severity.

The relationship of adverse events (AEs) with the CD133+ treatment will be evaluated by the investigator. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

All aspects of interest related to AEs will be collected and described using the following variables gathered by the physician/investigator:

- Type of event (AE, SAE, AR), categorical variable

- Maximum severity (non-serious, serious), categorical variable
- Description: signs, symptoms, pathology; categorical variables
- Duration and resolution (start and end dates), date format variables
- Maximum intensity (mild, moderate, severe), categorical variable
- Actions taken, treatment, and concomitant medication; categorical variables
- Causal relationship with the medication and/or study procedures, dichotomous variable (Yes/No)
- Outcome, categorical variable (ongoing/completed)
- Causality with the study drug, binary variable (Yes/No); and assessment of causality (definitive, probable, possible, unlikely, not related, unknown relationship), categorical variable.

The AE reporting period begins with the signing of the informed consent. Until the start of treatment with G-CSF, only SAEs caused by a protocol-required intervention (e.g., SAEs related to invasive procedures such as biopsies, medication washout) will be considered. The duration of the AEs will be specified, along with whether patients recover from them during the follow-up period.

All AEs will be characterized according to the occurrence date related to the visit. Any missing data on the start or end date of an AE will be related to the visit period (section 14, List of Tables and Figures, "Table V").

The start date/time of AEs will be compared with the date/time of the first administration of the study drug.

A confirmation of the absence of AEs is considered adverse event data.

If any deaths occur during the study, those patients will be included in the total number of exposed patients.

Laboratory evaluations

According to the parameters typically examined at the center, following the standard procedures for this type of treatment, and independent of what has already been performed by the Hematology Service during Visit 2, a complete blood count will be performed at the BST during Visit 4, after cell collection and selection.

Complete blood analysis: Biochemical, hematological, hemostatic, and serological. The biochemical analysis must include at least liver and kidney function (Total bilirubin < 1.5x normal reference values (NRV), AST and ALT < 2.5x NRV, and Serum Creatinine < 1.0 mg/dL; if the serum creatinine is > 1.0 mg/dL, then the estimated glomerular filtration rate (eGFR) should be >60 ml/min/1.73 m²). The serology should include at least the following tests: HIV 1 and 2 (Anti-HIV-1,2 antibodies), Hepatitis B (HBSAg, Anti-HBc), Hepatitis C (Anti-HCV antibodies; in cases of hematopoietic progenitors, PCR is also required), and Syphilis.
Blood group determination and autoimmune study (EAI).
Normal ranges in the first sample or analysis: These will be checked for the selection and eligibility criteria of patients based on baseline values in Visit 2 or in recent tests conducted within the last 30 days (before cell collection). A list of patients who do not meet the criteria will be produced.

Normal ranges in the first sample or analysis: Confirmation that parameters have returned to normal after cell mobilization. A list of patients with abnormal values after cell mobilization will be produced.

A list of these laboratory parameters will be provided. For each analysis, possible abnormal values will be identified and listed by patient specifically. Summary statistics will be produced in accordance with section 7.

Comparative analyses between the parameters collected before and after cell collection in the studied population may be considered according to section 8.3.

9.1.2 Descriptive Analysis of Adverse Events

The summaries of safety parameters related to the IMP (Investigational Medicinal Product) will be performed by the Safety Population. Only treatment-emergent adverse events (AEs) will be analyzed.

When calculating the incidence of adverse events by terms, or any subclassification of them by treatment, time period, severity, etc., each subject will be counted only once, and any repetition will be ignored; the denominator will be the total population size.

General descriptive summaries (Table V in "14 Listing of tables and figures") of safety endpoints will be performed for the total population exposed to the IMP and, if necessary, for relevant subgroups of interest (e.g., by instillation group). The main safety endpoints will be summarized with the number (%) of subjects having at least one AE. All safety data will be described, and summary statistics will be produced in accordance with Section 7, based on the general categories previously described in Section 9.1.2.:

- All adverse reactions
- Any AE (Adverse Event)
- Serious AEs
- Pre-treatment AEs
- AEs considered related to the IMP (Investigational Medicinal Product)
- AEs considered related to the procedures
- Late-onset AEs considered related to the IMP
- AEs requiring concomitant medication
- AEs considered related to G-CSF
- AEs leading to study treatment discontinuation and patient withdrawal related to the IMP
- AEs leading to study treatment discontinuation and patient withdrawal related to G-CSF
- AEs related to infusion
- Treatment-emergent AEs by preferred term, system organ class (SOC), and maximum severity. For each preferred term or SOC, multiple events in the same patient will be counted only once at the highest severity.

AEs will be summarized by SOC and preferred term. The number (%) of patients experiencing each event and the number of events will be summarized. Note: If a subject records multiple AEs with the same preferred term (i.e., with different start and end dates), these will be summarized once within the N (%) patient count, but each event will be counted within the number of reports (n) for each AE. Ongoing events will be counted only once.

Other safety parameters include:

- Study treatment compliance: In addition to general categories, a listing and summary table (Table VI in "14 Listing of tables and figures") with the incidences of AEs by preferred terms and/or SOC will be produced.
- All AEs, serious AEs, and AEs leading to withdrawal/termination or death will be highlighted and listed.

For the corresponding percentages, the denominator will be the respective number of exposed patients, i.e., patients who received the drug/IMP and were still in the study at that time or time interval, regardless of whether they had reported any AEs or attended visits.

For the primary objective, three sets are considered for the descriptive summaries (1) and (2).

1. **General AEs: throughout the study until month 15 post-treatment in the patient.**

Analyses will be conducted for the safety/ITT population, for the general population, and for specific groups of interest.

Incidence, prevalence, and frequency measures of adverse events (AEs) will be calculated at the end of the study (month 15 post-treatment of the patient).

Descriptive summaries will be produced for all categories of adverse events until the end of the study (month 15 post-treatment of the patient).

2. **AEs in the case of full-term pregnancy: AEs that may occur during pregnancy, delivery, and the postpartum period.**

A subset of exposed patients consisting of those with a full-term pregnancy. Analyses will be conducted for the safety/ITT population, for the general population, and for specific groups of interest.

Incidence, prevalence, and frequency measures of adverse events (AEs) will be calculated in three stages: during pregnancy, during delivery, and in the postpartum period.

General descriptive summaries will be produced for this subset for all categories of adverse events. Additionally, the same descriptive summaries will be produced for the three stages: during pregnancy, during delivery, and in the postpartum period.

3. **AEs in the case of live newborns (LNs): adverse events that may be related to the investigational product (IP) up to the first month of life.**

A subset of exposed patients consisting of those with a full-term pregnancy and at least one live newborn. Analyses will be conducted for the safety/ITT population, for the general population, and for specific groups of interest.

Incidence, prevalence, and frequency measures of adverse events (AEs) will be calculated for the patients in this subset and for the live newborns.

General descriptive summaries of the patients in this subset will be produced up to the newborn's first month of life for all categories of adverse events. Additionally, the same descriptive summaries will be produced for the live newborns up to their first month of life.

9.2 Secondary Analysis: Efficacy

The functionality of the treated endometrium will be evaluated by the secondary efficacy endpoints in patients who wish to conceive after therapy with CD133+.

Summaries will be produced according to Section 7 for all variables of interest and efficacy endpoints; the data will be presented for each patient, summarized by population and/or subgroup. Statistical evaluation, test statistics, necessary statistical assumptions, and significance level will be performed according to Section 8 (8.1, 8.2, and 8.3). The analyses of the secondary objectives are mainly hypothesis-generating. P-values for selected efficacy analysis will be presented for exploratory purposes. The efficacy of the objectives will be analyzed using contrasts, statistical tests, and modeling, as well as descriptive statistics, frequency tables, and cross-tabulations. The safety population is considered the primary analysis population, but since there may be patients who do not undergo embryo transfer, there is likely to be a loss of power in this population for endpoints involving the ART outcome and gestational follow-up. Analyses will be conducted in the safety population and repeated using the per-protocol and ITT populations as robustness measures.

Since this treatment is administered only once and the temporal course and duration of effect are unknown, all secondary analyses will be evaluated according to the relevant endpoint between Visit 6/V_{FP} and V_{TRA} and Follow-up/V_F.

9.2.1 Results of Assisted Reproductive Technology (ART) and Pregnancy Follow-up

The Live Birth Rate (LBR) for the exposed population and the per-protocol population will be evaluated as the primary efficacy endpoint, in addition to other parameters of interest as outcomes of ART:

- The implantation rate (IR) per embryo transferred,
- Pregnancy rate (PR) per transfer and per patient,
- Ongoing pregnancy rate (OPR) per transfer and per patient.

Results will be described for each patient, and the parameters of interest will be summarized for all patients by populations and by possible groups of interest (e.g., groups by millions of cells infused).

The descriptive summary will be completed with other gestational follow-up endpoints:

- Clinical miscarriage rate (CMR)
- Biochemical pregnancy rate (BPR)
- Ectopic pregnancy rate (EPR)

9.2.2 Hysteroscopic Score

The hysteroscopic score will be described by patient, and the grades of Asherman syndrome will be analytically compared in the population set, before and 28 days after treatment.
To compare the ordinal measure of the grade of Asherman for two related samples (before vs. 28 days after), the Wilcoxon test for related samples will be used, or the paired t-test if the necessary assumptions are met.

9.2.3 Endometrial Thickness and Pattern

The results—endometrial pattern and thickness—will be described by patient and summarized by populations before and after treatment. If necessary, subgroups will also be included. Summaries will be produced in accordance with section 7.

The results of hysteroscopic tests in the analyzed population will be compared, using quantitative and dichotomous variables, before and after treatment with IGX1 across all patients to assess potential improvement.

Due to differences in endometrial status in the pre-treatment measurements, where at Visit 3 the endometrial thickness will be at a maximum state due to hormonal treatment, two comparisons will be made: the measurement at Visit 1 versus the post-treatment visit, and the measurement at Visit 3 versus the post-treatment visit.

Thickness comparisons will be made using the paired t-test for two related samples (pre-treatment vs. 28 days after)—the Wilcoxon non-parametric test will be used if the necessary assumptions are not met. For the endometrial pattern as a dichotomous variable, the McNemar test or the exact McNemar test will be used for repeated measures.

Descriptively, for patients who do not undergo ART or become pregnant, follow-up visits will assess endometrial thickness and pattern.

9.2.4 Recovery of Endometrial Volume

The results of the endometrial volume criterion measured by 3D ultrasound in cm^3 will be described by patient and summarized by populations before and after treatment. If necessary, subgroups will also be included. Summaries will be produced in accordance with section 7.

The results of endometrial volume as a quantitative variable in the analyzed population will be compared before and after treatment with IGX1 across all patients to assess potential improvement.

Due to differences in endometrial status in the pre-treatment measurements, where at Visit 3 the endometrial volume will be at a maximum state due to hormonal treatment, two comparisons will be made: the measurement at Visit 1 versus the post-treatment measurement and the measurement at Visit 3 versus the post-treatment visit.

Comparisons will be made using the paired t-test for two related samples (pre-treatment vs. 28 days after)—the Wilcoxon non-parametric test will be used if the necessary assumptions are not met.

Descriptively, for patients who do not undergo ART or become pregnant, follow-up visits will assess endometrial volume.

9.2.5 Endometrial Vascularization via Biopsy

Vascular formation by CD133+ will be evaluated using digital histology or immunofluorescence with the α-SMA marker in paraffin-embedded endometrial sections fixed in formalin. By comparing the samples before and after treatment, a visual observation can indicate whether there has been an increase in α-SMA or blood vessels, which would suggest greater vascularization.

Data will be presented as specific values for each patient before and 28 days after cell therapy, as well as mean values with associated standard error of the mean (SEM).

The dynamics of the total number of mature blood vessels in patients before and 28 days after, as well as during subsequent follow-up visits of cell therapy, will be graphically represented (14 List of Tables and Figures, "Figure I"), indicating a time-sensitive neoangiogenic effect, along with the corresponding means and associated standard errors (SEM).

Results will be compared between the start of the experiment (control) and 28 days after treatment with CD133+ cells using the corresponding means and SEM. Comparisons will be made using the paired t-test for related samples (control vs. 28 days after)—the Wilcoxon non-parametric test will be used if the necessary assumptions are not met.

9.2.6 Return of Menstrual Cycles

Evaluate the recurrence of menstrual episodes (if there were none before treatment) or compare differences in onset, duration (in days), and quantity (in number of pads/days) after treatment with embryonic stem cells up to the embryo transfer, regarding the menstrual episodes prior to treatment.

The mean value will be taken for pre-treatment and post-treatment for duration in days and for pads/days before the initiation with the PEI. Compare the pre-treatment period with the post-treatment period of the CD133+ cell treatment in the studied population. Comparisons will be made using the paired t-test for related samples—the Wilcoxon non-parametric test will be used if the necessary assumptions are not met.

Summaries will be produced in accordance with section 7 for the duration, quantity, and frequency of menstruation before and after treatment with the PEI, and will be graphically represented with box plots (14 List of Tables and Figures, "Figure II").

9.2.7 Determine the Dose at Which It Is Possible to Distinguish Between Pregnancy and Non-Pregnancy

Determine the cell dose, the cutoff point for the number of CD133+ cells, from which it is possible to discriminate between pregnancy/no pregnancy (response variable) according to the established minimum quality requirements (sterility, cell viability greater than or equal to 50%, and purity greater than or equal to 70%), allowing for the determination of the sensitivity and specificity of the product before its use.
The minimum effective dose and the maximum safe dose are still unknown.

In cases where the minimum quantity (≥30x10^6) is not reached and provided the PEI meets the other quality requirements for infusion, the patient may receive treatment with IGX1 even if the dose is below the indicated minimum. The results for this patient will not be included in the per-protocol population but will be included for the other population groups. If the patient does not accept, they will be excluded from the study. The eventual occurrence of adverse events will be monitored according to the established protocol.

Compliance with the established minimum quality requirements:

Cell viability greater than or equal to 50% (Yes/No)
Purity greater than or equal to 70% (Yes/No)
Sterility (Yes/No)
Dose below the indicated minimum (Yes/No)
Patients who do not meet the minimum quality requirements will be excluded from the per-protocol analysis.

In addition to the characteristics that the PEI must meet as mentioned, the following will be controlled:

Total number of CD133+ stem cells in millions [≥30x10^6, ≤236x10^6]
Final volume in milliliters of IGX1 infused.
Number of syringes administered. One syringe (with a maximum volume of 50ml) containing CD133+ cell concentrate is approximately 30-50 ml. Occasionally, more than one 50 ml syringe may be administered if a larger volume is obtained based on the mobilization of stem cells, always infused at the same time.
Route of administration: intra-arterial
Administration time: within the first 24 hours after processing (preparation and selection) (Yes/No)

A descriptive list will be made by patient of the characteristics of the PEI, and summaries will be provided by population set and subgroups according to section 7.

Total Dose of CD133+ Cells in Pregnancy vs. No Pregnancy

The most prudent approach to presenting data in dose discrimination studies is to fully explain, describing the effects on subjects and/or statistically, the behavioral effect of the CD133+ test agent on all subjects, individually and/or as a group.

Establish a minimum and maximum safety range determined by the occurrence of adverse events with a pre-specified severity (AE or SAE); and treatment effectiveness determined by pregnancy/no pregnancy outcomes.

Identify the mean dose (x10^6) of total cells and the dose volume (mean ± standard deviation, range, maximums, and minimums) in mL infused, according to the reproductive outcome criterion. By separating pregnancy/no pregnancy, we will attempt to determine a discriminative amount of total cells. For comparisons, we will use the non-parametric U-Mann Whitney test for two groups for independent, unpaired samples—a Student's t-test for independent samples if the necessary assumptions are met.

GLM Model and Optimal Dose

Fit a Generalized Linear Model for Logistic Regression. The model where the independent variable X ≥ 0 refers to the total dose of CD133+ cells in mill/ml; while the dependent variable, response, or effect Y will be binary: pregnancy / no pregnancy. This function provides an analysis to fit the sigmoid dose-response curves.

Graph of the probability of pregnancy versus the total dose of CD133+ cells.

Estimate effective doses (ED50) with their standard errors and 95% confidence intervals. Values (with a 95% CI) of the dose variable corresponding to a series of probabilities of interest will be calculated.

Exploratorily, a model will be developed to determine an optimal cutoff point for both the efficacy endpoint of pregnancy and the safety endpoint (SAE), with the intention of detecting possible differences that may lead us to generate new hypotheses.

Calculate the ROC curve, area under the curve (AUC), optimal cutoff point, sensitivity, and specificity for the fitted model. For the study parameter, the ROC curve will represent sensitivity against 1 minus specificity for a range of parameter threshold values. The area under the ROC curve (AUC) will be calculated along with 95% confidence intervals as an indicator of overall diagnostic performance.

We will rely on visual verification of the fitted curves along with the observed proportions. A plot of the original data with the fitted dose-response curve(s) will provide a visual impression of how well the model fits the data.

9.2.8 Evaluate and Describe the Quality of Life (QoL) of the Participating Patients

Evaluate quality of life (QoL) using a validated measurement tool (FertiQoL) in infertile patients with Asherman syndrome before treatment with IGX1 and during the first cycle of IVF/ICSI, with complementary assessment of changes in FertiQoL scores after the first cycle.

Summary tables will be created before and after treatment for each question and subscale in accordance with section 7. A summary table (14 List of Tables and Figures, "Table VII") will present the total scores and subscale scores from the questionnaires according to section 7, prior to treatment and after the outcome of the IVF/ICSI cycle, along with p-values. If deemed appropriate, a bar graph will represent the mean FertiQoL scores before and after treatment, with error bars representing standard deviations.

Compare the mean total FertiQoL score of patients at the start of IGX1 treatment with the score at the end of IGX1 treatment and the IVF/ICSI cycle. Assess whether the mean FertiQoL changed after the first treatment with IGX1 and the IVF/ICSI cycle.

For the analysis of FertiQoL scores before treatment versus after treatment and ART, a paired t-test will be used for related samples—the Wilcoxon non-parametric test will be applied if the necessary assumptions are not met. The Cronbach's α reliability coefficients will be calculated to assess the reliability of the FertiQoL tool.

9.3 Exploratory Analysis

9.3.1 Study of the Endometrial Receptivity Profile

Study of the Endometrial Microbiome to Establish its Possible Impact on Asherman's Syndrome and its Relationship with Assisted Reproduction Treatment Outcomes, Using Next-Generation Sequencing (NGS) Technologies to Compare the Microbial Profiles of Endometrial Fluid and Biopsy.

The analysis of the endometrial microbiome will be based on the population exposed to the treatment, including ITT/safety and per protocol populations, which consist of all patients who underwent the treatment and from whom we obtained the necessary samples for follow-up.

The endometrial microbiome profile will be described for each patient before and after treatment. Patients will be summarized both before and after treatment according to the ITT/Safety and per protocol populations, as outlined in section 7.

Those patients whose microbiological profile changes in the second biopsy/first post-treatment biopsy compared to the pre-treatment profile will be identified.

Comparisons of endometrial profiles will be made between paired related samples (before vs. after treatment). To compare the observed proportion of a variable classified into more than two categories (k=3 categories) with two dependent samples, the McNemar-Bowker test will be used to determine whether the treatment induces a change in the categorized response of the endometrial profiles subjected to it. If the biological profile variable has only two categories, the McNemar Exact Test will be used.

9.3.2 Study of the Endometrial Microbiome

9.3.3 Histological Study

Histological study of endometrial biopsies before and after stem cell treatment to compare differences in endometrial structure and tissue regeneration mechanisms in order to evaluate possible mechanisms of action.

The analysis will be based on the population exposed to the treatment, including ITT/safety and per protocol populations, consisting of all patients who underwent the treatment and from whom we obtained the necessary samples for follow-up.

Endometrial structure will be described for each patient before and after the treatment. Patients will be summarized both before and after treatment according to the ITT/Safety and per protocol populations, in accordance with section 7.

Comparisons of endometrial structure will be made for the entire cohort for related samples of the before-and-after treatment type. The non-parametric Wilcoxon test will be used to compare percentages of cells in women before and after treatment.

10 Software

The SPSS software for social sciences (IBM Corp., USA) and R version 3.6.1 will be used for statistical analyses.

11 Annexes

Annex A: Imputation of Partially Missing Data for Adverse Events

This algorithm will be used to impute the start dates of conditions and adverse events (AEs) that already exist for which only partial information is available. For ease of reference, all events, whether pre-existing or emerging during treatment with the PEI, are referred to as AEs. The start dates of AEs should be imputed before imputing the end date in all cases. The end date of an AE should only be used for imputing the start date if it is a known and complete date.

If the start and/or end date of an AE is only partially unknown, the AEs will be characterized as emerging, before, during, or after treatment based on the period or visit in which they are recorded.

When imputing start dates, if the day and month of the AE are missing:

If the year is the same as the year of the PEI dose:The start date of the AE will be imputed as the first day of the period marked by the corresponding visit.

If the year is earlier than the year of the PEI dose: The start date of the AE will be imputed as the first day of the period marked by the visit, up to December 31.

If the year is later than the year of the PEI dose: The start date of the AE will be imputed as the first day of the period marked by the visit, at least January 1.

When imputing start dates, if only the month of the AE is missing:

- If the period marked by the visit includes more than one month, treat the day as missing and impute both following the practice described above "if the day and month of start are missing"; if the period marked by the visit encompasses a single month, impute the month of the visit in which it was recorded.

When imputing start dates, if only the day of the AE is missing:

- Impute the first day of the period marked by the visit; if the period includes more than one month, impute the first day of the month recorded in the partially known date of the AE.

When imputing end dates, if the day and month of the AE end are missing:

- If the year is the same as the year of the PEI dose:

The end date of the AE will be imputed as the last day of the period marked by the corresponding visit.

- If the year is earlier than the year of the PEI dose:

The end date of the AE will be imputed as the last day of the period marked by the visit, up to December 31.

- If the year is later than the year of the PEI dose:

The end date of the AE will be imputed as the last day of the period marked by the visit, at least January 1.

When imputing end dates, if only the month of the AE is missing:

- If the period marked by the visit includes more than one month, treat the day as missing and impute both following the practice described above "if the day and month of start are missing"; if the period marked by the visit encompasses a single month, impute the month of the visit in which it was recorded.

When imputing end dates, if only the day of the AE is missing:

- Impute the last day of the period marked by the visit; if the period includes more than one month, impute the last day of the month recorded in the partially known date of the AE.

If both the start and end dates of an AE are completely unknown, the AE will be considered as emerging during treatment. However, this is not considered feasible as all visits marked on the calendar are necessary for the continuation of treatment.

12 Apendix

Apendix A: Table of study visits

	SELECTION AND EVALUATION	OPEN TREATMENT AND REGENERATION					TRA and follow up	
Visits programme and evaluations	**Basal visit**	**Hematology evaluation, start treatment with G-CSF**	**Endometrial diagnosis pretreatment and cellular mobilization**	**Recollection and cellular selection**	**Instillation**	**Endometrial diagnosis post treatment and final visit post treatment**	**TRA and follow up/final visit**	**Non programmed visits**
	Vb/V1 Day -45 to 1*		**V3 Day 7 (+1)**	**V4 Day 8 (+1)**	**V5 Day 10 (+1)**			
		V2 Day 1*				**V6/VFP Day 37 (±7)**	**VTRA and follow up/VF day 50 (±7) until month 15 (±1)**	
Inclusion/Exclusion criteria[A,B,1]	X	X						
Signature [A,B,2]	X							
Clinical history and demographical data[A,B]	X	X						
Previous medication[A,B,3]	X	X						
Physical exploration and vital constants[A,B,4]	X	X	X	X[i]	X[i]	X		X
Full blood analysis tests (biochemical, haematological, serological, hemostasia) [A,B,C,5]		X						X
Blood group and EA[B]		X						
Pregnancy test in blood (β-HCG) [A,B,6]		X					X	X
ECOG[B]		X						
ECG and thorax radiography[A,B,7]	X	X						
Estradiol and progesterone regimen[A,B]	X		X[iv]				X[iv]	X
Assessment of vascular access (arterial and venous) for catheterization and apheresis[B,C,9]		X		X	X			
ECO 2D/3D[A,10]	X		X			X	X	X
Menstrual calendar[A,11]	X						X	
FertiQol Questionaire[A,12]	X						X	
Prescription, collection and treatment with G-CSF for mobilization of CPSP[B,13]		X	X	X				
HSC[A,14]			X			X		
Collection of LE for microbiome[A,15]			X			X		X
Test ERA/Biopsy[A,16]			X			X		X
Patient evaluation[A,B,C]	X	X	X	X	X	X		X
Return of G-CSF[B,17]				X				
HSPC collection/apheresis[B,C,18]				X				
Shipment of the unit[B,C,19]				X	X			
Preparation and selection of CD133 and instillation of IGX1 (catheterization)[B,C,20]					X			

* Two independent visits are considered as they take place in different centers, even if they coincide on the same day (Day 1 of the study). The procedures performed at both visits are complementary to each other..
[A] Procedure performed at Hospital del Pilar and/or Hospital Quirónsalud in Barcelona, both part of the Quirónsalud Group.
[B] Procedure performed at Hospital Universitario Vall d´Hebrón (HUVH).
[C] Procedure performed at Centro de Procesamiento: Banc de Sang i Teixits (BST).
[1] The patient must meet all inclusion criteria and none of the exclusion criteria. The study selection criteria will be verified at both Quirónsalud centers and HUVH as indicated in section 6
[2] Consent must be signed before performing any test or specific procedure of the protocol that is not part of the center's routine practice.
[3] Medication taken in the last 30 days before the patient enters the study and previous medication continuing at the time of study entry.
[4] Includes temperature, blood pressure, pulse, respiratory rate, weight, height, and BMI as per the center's routine practice.
[i]. Measured just before and after apheresis. Includes at least blood pressure and pulse.
[ii] Measured just before and after the stem cell instillation (upon admission and 2 hours after the instillation). Includes at least blood pressure, heart rate, and dorsalis pedis pulse, as per the routine practice of the Radiology Department at HUVH.
[5] According to the parameters typically examined at the center. In visit 2, biochemical analysis must include at least liver and kidney function (Total bilirubin < 1.5xULN, AST and ALT < 2.5xULN, and Serum Creatinine < 1.0 mg/dL; if serum creatinine is > 1.0 mg/dL, then the estimated glomerular filtration rate (eGFR) should be >60 ml/min/1.73 m2). Serology must include at least the following tests: HIV 1 and 2 (HIV-1,2 Antibodies), Hepatitis B (HBSAg, Anti-Hbc), Hepatitis C (Anti-HCV Antibodies; in cases of hematopoietic progenitors, PCR is also required), and Syphilis. Recent tests within the last 30 days will be accepted.
[iii] Following the center's usual procedures for this type of treatment, and independent of the one already performed by the Hematology Department in visit 2, a complete blood count will be done at BST before and after cell collection.
[6] A blood pregnancy test (β-hCG) will be done at HUVH in visit 2 (mandatory in all cases) and at the relevant ART visit at a Quirónsalud Group clinic if ART is performed within the first 6 months) following the center's usual practice (approximately 10-14 days after embryo transfer: β-hCG result visit).
[7] Tests performed within 6 weeks prior to selection are acceptable
[8] Patients who have started treatment with estrogens and progesterone following the center's usual practice within the 2 weeks prior to study entry will be accepted
[iv] Initiation of hormone replacement therapy (HRT) before performing the ERA test following the usual clinical practice for both V3 and VTRA/VF
[9] Performed by the Radiology and Hematology Departments at HUVH and/or BST
[10] Diagnostic 2D/3D ultrasound in the Proliferative Phase at visit 1, 2D/3D ultrasound at visit 3 after four days of G-CSF treatment and before apheresis, and 2D/3D control ultrasound at visit 6 (VFP), coinciding with the second HSC after being on HRT treatment, approximately three weeks after instillation and after the patient has been deprived of menstruation. In case of ART, as per usual clinical practice, a 2D/3D ultrasound will also be performed at VTRA and Follow-up / VF just before embryo transfer, as well as the corresponding gestational ultrasounds (weeks 12-14, 22-24, and 34-36) in the case of an evolving pregnancy.
[11] At the patient's entry into the study at V1/Vb and at VTRA and Follow-up / VF at the end of the 6 months after ART
[12] At the patient's entry into the study at V1/Vb and at VTRA and Follow-up / VF at month 15.
[13] The G-CSF collection will be done at the Pharmacy Department at HUVH in Visit 2 after evaluation and prior prescription by the hematologist from the Hematology Department at HUVH, preferably on a Tuesday. The patient will begin treatment at home on Day 4(+1), preferably Friday or Saturday, depending on the week, for 5 consecutive days at a dose of 10 µg/kg every 24 hours, always following the instructions of the hematologist and Pharmacy at HUVH. The patient will continue with home treatment on Days 5(+1) and 6(+1), Saturday and Sunday or Sunday and Monday, depending on the start date.
[14] A diagnostic hysteroscopy will be performed in visit 3 after treatment with estradiol and progesterone following the usual clinical practice before apheresis and in visit 6 / VFP (control after treatment), after HRT following the usual clinical practice, on Day 37(±7) approximately 3 weeks after instillation and after the patient has been deprived of menstruation
[15] An LE sample will be taken immediately before obtaining the BE for the ERA test on Day 5 of HRT, following the usual clinical practice as indicated.
[16] A diagnostic ERA test will be performed in visit 3 after treatment with estradiol and progesterone following the usual practice before apheresis and in visit 6 / VFP (control after treatment), after HRT following the usual clinical practice, on Day 37(±7) approximately 3 weeks after instillation and after the patient has been deprived of menstruation. In Visit 3, the result of an ERA test performed within the 2 years prior to the patient's inclusion in the study may be accepted
[17] The return of the used drug may be done directly at the Pharmacy Department at HUVH or to the personnel of the Hematology Department at HUVH, before or after starting apheresis, as indicated by the center's investigator.
[18] The patient will be admitted in the morning for the apheresis process. She will be discharged the same day after observation, following the usual practice (6-8 h).
[19] In Visit 4, the unit (plasma volume ranging from 200-500 ml, depending on the patient) will be sent from HUVH to BST. In Visit 5, the resulting unit after preparation and cell selection (drug already prepared for instillation) will be sent from BST to HUVH
[20] Preparation and cell selection at BST on Day 9(+1), within 24 hours prior to instillation, preferably on Wednesday or Thursday. The instillation (catheterization) of IGX1 will take place at the Radiology Department at HUVH after evaluating the patient within the first 24 hours after the IGX1 processing is completed. The patient will be discharged the same day after observation, following the usual practice (6-8 h).
[21] At the end of Visit 5, the patient will be given a diary to facilitate the recording of AEs and Concomitant Medication. This will be reviewed in Visit 6 / VFP and subsequent follow-up visits, either in person or by phone, as well as in unscheduled visits, until the Final Visit of the study at month 15, when it will be returned.
[22] ART within the first 6 months after V6 / VFP in patients planning to undergo a single embryo transfer (SET) of frozen embryos in a substituted cycle (HRT) following the usual clinical practice. Exceptionally, cases of double embryo transfer (DET) may be accepted if medically indicated. During these first 6 months, the patient may undergo one or more ART procedures (in case of negative β-hCG or ectopic pregnancy, biochemical or clinical miscarriage after treatment and recovery), always following the usual clinical practice. This visit spans from Visit 6/VFP to VF (maximum month 15). In case no ART is performed in the first 6 months, the patient will be part of the safety and efficacy population, with follow-up visits at months 9, 12, and 15 (VF). If ART is performed in the first 6 months, a β-hCG result visit will be scheduled following the usual practice (approximately 10-14 days post-transfer). In case of an evolving pregnancy, gestational follow-up visits will be scheduled, coinciding with the usual practice, i.e., at weeks 12-14, 22-24, and 34-36. In the case of a live birth, postnatal follow-up of the newborn will

be done 1 month after birth (VF), which may coincide with the VF at month 15 or, if the baby is born before month 15, follow-up will always continue until month 15 itself. If there is no evolving pregnancy, follow-up visits will be done at months 9, 12, and 15 (VF).
23 From the start of G-CSF® on Day 4(+1) to the Final Visit of the study at month 15(±1).

13 References

1. Boivin J, Takefman J, Braverman A. The fertility quality of life (FertiQoL) tool: development and general psychometric properties, *Hum Reprod*, 2011, vol. 26 (pg. 2084-2091)
2. Santamaria X, Cabanillas S, Cervelló I, Arbona C, Raga F, Ferro J, Palmero J, Remohí J, Pellicer A, Simón C. Autologous cell therapy with CD133+ bone marrow-derived stem cells for refractory Asherman's syndrome and endometrial atrophy: a pilot cohort study. Hum Reprod. 2016 May;31(5):1087-96. doi: 10.1093/humrep/dew042. Epub 2016 Mar 22.

14 Tables y figures

Table I Demographic and clinical characteristics of the patients at baseline*.

Patient	Preoperative menstrual history	Etiology of Asherman	Prior repair attempts	Age	Maximum preoperative endometrial thickness (mm)	Hysteros copy 1 Before cell therapy	Hysteros copy 2 Before cell therapy	Hysteros copy 3 After cell therapy	Post-operative menstrual history	Maximum post-operative endometrial thickness (mm)	Pregnancy outcome
1											
2											
...											
n											

Table II Patients treatment.

Patient	Number of cells inyected (in millions)	cell viability (%)	cellular purity (%)	IGX1 dose (ml)	Pregnancy outcome
1					
2					
...					
n					

Table III Concomitant medication.

ATC Class Preferred Term	IGX1 treatment (N=)
Any concomitant medication	(n) (%)
ATC Class	
Preferred Term	
Concomitant medication for Severe AE	
ATC Class	
Preferred Term	

Table IV Clinical history.

Preferred Term (SOC)	IGX1 treatment (N=)

Comentado [LP1]: Modificar este apartado incluyendo un listado de tablas o eliminar apartado.

Comentado [DV2R1]: De acuerdo, se pueden eliminar ya que eran ejemplos.

Comentado [LP3]: esto no es una tabla sino un listado.

Comentado [LP4]: no se puede dar el máximo porque se recoge un único valor basal

Comentado [LP5]: a qué se refiere esta variable exactamente?

Comentado [LP6]: WHO

Comentado [LP7]: MedDRA

Any Prefered Term (SOC)	(n) (%)
Preferred Term$_1$ (SOC$_1$)	
…	
Preferred Term$_n$ (SOC$_n$)	

Table V Safety Overview.

Participants experiencing at least one:	**IGX1 treatment (N=)**
Any Adverse Reaction	(n) (%)
Any Adverse Event	
AE related to G-CSF	
Severe AE	
AE related to IGX1	
Severe AE	

Table VI Frequency of AEs.

System Organ Class (SOC) **Preferred Term (PT)**	**IGX1 treatment (N=)**
SOC$_1$	(n) (%)
PT$_1$	
…	
…	
SOC$_n$	
PT$_n$	

Table VII Unadjusted total and subscale scores of the FertiQoL and SCREENIVF questionnaires.

Characteristics	**Pre-treatment (N=)**	**Post-treatment (N=)**	**P-value**
Core subscales	Mean (sd) Median (range)	Mean (sd) Median (range)	
Emotional			
Mind-Body			
Relational			
Social			
Core FertiQoL			
Treatment subscales			
Treatment Environment			
Treatment tolerability			
Treatment FertiQoL			

Total FertiQoL

Figure I Tissue analyses. (Simón C. et al. 2016)

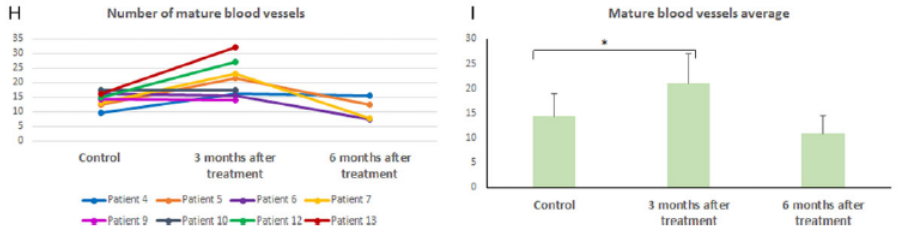
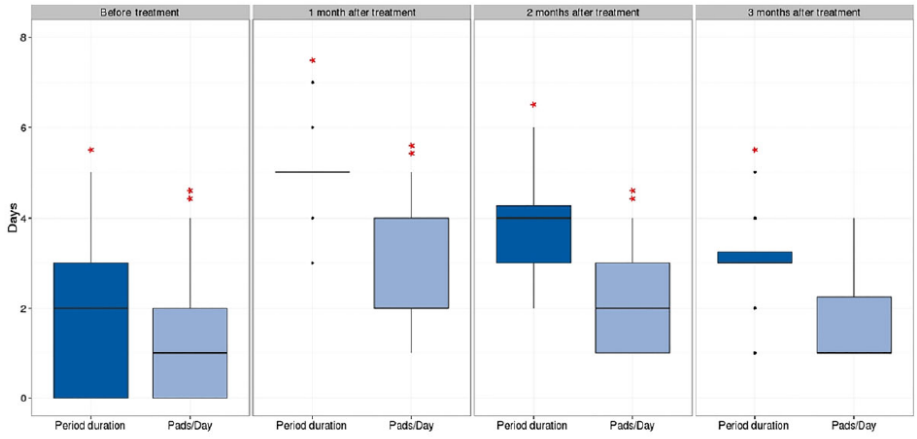


Figure II Duration and intensity of menses in days and number of pads from the month before up to the third month after cell therapy. (Simón C. et al. 2016)



	Before treatment	1 month after treatment	2 months after treatment	3 months after treatment
Period duration	1.94 ± 1.69	5.06 ± 0.85	3.81 ± 1.05	3.25 ± 1.06
Pads/day	1.19 ± 1.10	2.69 ± 1.19	2.12 ± 0.96	1.75 ± 1