CLINICAL STUDY PROTOCOL

Title:	A Phase 1/2 Study of a Combination of FCX-013 (Genetically-Modified Autologous Human Dermal Fibroblasts) plus Veledimex for the Treatment of Moderate to Severe Localized Scleroderma (Morphea)
Protocol Number:	FI-SC-001
Sponsor:	Fibrocell Technologies, Inc. 405 Eagleview Boulevard Exton, PA 19341
Investigational Product:	FCX-013
Protocol Version/Date:	Version 2.0, 10 August 2020

GCP Statement

This study will be conducted in accordance with the United States (US/USA) Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) guidelines on current Good Clinical Practice (GCP) in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and relevant country-specific regulatory requirements of the country in which the research will be conducted.

1. SIGNATURES

Title:	A Phase 1/2 Study of a Combination of FCX-013 (Genetically-Modified Autologous Human Dermal Fibroblasts) plus Veledimex for the Treatment of Moderate to Severe Localized Scleroderma (Morphea)
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Sponsor's Approval

The protocol has been approved by Fibrocell Technologies, Inc. (Fibrocell).

Sponsor's Authorized Officer:

Mary Spellman, MD Chief Medical Officer	Date

Investigator's Agreement

Title:	A Phase 1/2 Study of a Combination of FCX-013 (Genetically-Modified Autologous Human Dermal Fibroblasts) plus Veledimex for the Treatment of Moderate to Severe Localized Scleroderma (Morphea)
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I have read and understood the contents of the protocol FI-SC-001.

- I agree that the Protocol contains all of the information necessary to conduct the study.
- I agree to conduct the study as outlined herein and in accordance with ICH guidelines on current GCP, with applicable US FDA regulations set forth in 21 CFR parts 50, 54, and 312, and all other relevant country-specific regulatory requirements of the country in which the research will be conducted.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligation and comply with the study protocol.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Principal Investigator's Name (Printed)

_____ _____

Principal Investigator's Signature Date

2. SYNOPSIS

Name of Sponsor/Company: Fibrocell Technologies, Inc. (Fibrocell)		
Name of Investigational Product: FCX-013 + veledimex (FCX-013 plus veledimex)		
Name of Active Ingredient: FCX-013 (Genetically Modified Autologous Human Dermal Fibroblasts) Veledimex capsules for oral administration		
Protocol Number: FI-SC-001	**Phase:** 1/2	**Country:** USA
Title of Study: A Phase 1/2 Study of a Combination of FCX-013 (Genetically-Modified Autologous Human Dermal Fibroblasts) Plus Veledimex for the Treatment of Moderate to Severe Localized Scleroderma (Morphea)		
Study center(s): Up to 3 centers		
Studied period (years): Estimated date first subject screened: 4Q2019 Estimated date last subject completed: 2035 (includes long-term follow-up)		**Phase of development:** I Phase 1/2
Objectives: **Primary:** The primary objective of this protocol is to evaluate the safety of FCX-013 plus veledimex in subjects with moderate to severe localized scleroderma/morphea. **Secondary:** The secondary objective of this protocol is to evaluate the antifibrotic effects of FCX-013 plus veledimex via the LoSCAT (Localized Scleroderma Assessment Tool) and durometry.		
Methodology: This is an open-label, single arm Phase 1/2 study being conducted by Fibrocell to evaluate FCX-013 in subjects with moderate to severe localized scleroderma. Approximately ten subjects will be enrolled and receive FCX-013. The study is divided into the following periods: Screening (including Manufacturing of FCX-013), Treatment, and Long-Term Follow-Up. The Screening Period consists of evaluation of eligibility, the collection of one set of three 3-4 mm biopsies for the manufacture of FCX-013 product, and the identification of potential target sclerotic lesions. Due to the FCX-013 manufacturing process, the Screening Period is expected to have a duration of approximately 4-6 months; however, this period can be extended to accommodate subject scheduling, variations in manufacturing duration and protocol mandated delays (i.e. pauses due to staggered treatment).		

After FCX-013 manufacturing is complete, Fibrocell (the Sponsor) and the Investigator will mutually agree on the planned date for injection of FCX-013.

The Treatment Period will have a 2-week duration. One administration of FCX-013 will consist of a maximum of 4 mL of FCX-013 administered in up to sixteen (16) 0.25 mL intradermal injections. On Day 1, FCX-013 will be intradermally injected, using a retro-tracing technique, into the sclerotic lesion targeted for treatment. On Day 1, following the injection of FCX-013, subjects will initiate a 14-day course of veledimex to be taken orally daily.

Administering FCX-013 following each of the first three subjects requires that the previous subject complete Week 4 evaluations, and that the Investigator(s) must have received approval from the Data Safety Monitoring Board (DSMB).

The End of Treatment visit is at Week 12.

Safety and clinical efficacy evaluations are conducted throughout the study. Safety will be assessed through adverse events (AEs), physical examinations, vital signs, clinical laboratory evaluations, electrocardiograms (ECGs) and concomitant medications.

The Long-Term Follow-Up period is an approximately 15-year period following the End of Treatment in which safety is monitored annually.

Number of subjects (planned):

Approximately 10

Diagnosis and main criteria for inclusion:

Adults with a clinical diagnosis of any subtype of moderate to severe localized scleroderma/morphea with sclerotic lesions.

Investigational product, dosage and mode of administration:

- FCX-013 via intradermal injection
- Veledimex capsule for oral administration

One administration of FCX-013 will consist of a maximum of 4 mL of FCX-013 administered in up to sixteen (16) 0.25 mL intradermal injections. On Day 1, FCX-013 will be intradermally injected, using a retro-tracing technique, into the sclerotic lesion targeted for treatment. On Day 1, following the injection of FCX-013, subjects will initiate a 14-day course of veledimex to be taken orally daily.

Reference therapy, dosage and mode of administration:

Not applicable.

Criteria for evaluation:

Safety: Safety will be assessed through AEs, physical examinations, vital signs, clinical laboratory evaluations, ECGs, and concomitant medication use. Analysis of replication-competent lentivirus (RCL) antibodies will also be performed.

Efficacy: Clinical evaluation of antifibrotic effects via durometry evaluation and LoSCAT (Localized Scleroderma Assessment Tool).

Quality of life will be assessed using the SkinDex 29+3.
Statistical methods: Descriptive statistics are planned for this study. **Safety:** Safety evaluations will be based on listed AEs, physical examinations, vital signs, clinical laboratory evaluations, ECGs and prior/concomitant medications, and assessment for the presence of RCL antibodies. The AE severity will be described using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grades, using the current version at study start. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 23.0 or later) and described by body system and preferred term, relationship to FCX-013, seriousness, and severity. AEs causing investigational product discontinuation and/or early study discontinuation, and serious adverse events (SAEs) will be noted. **Efficacy:** All subjects who were administered FCX-013 and had at least one assessment of the target lesion post-administration will be included in the efficacy population. The change from baseline in the LoSCAT and durometry scores will be reported descriptively, as will changes in the SkinDex 29+3 scores. The primary method of handling data will be last observation carried forward (LOCF).

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LIST OF TABLES

4. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALT/SGPT	Alanine Aminotransferase
AST/SGOT	Aspartate Aminotransferase
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture
FAS	Full Analysis Set
FCX-013	Genetically-Modified Autologous Human Dermal Fibroblasts (product -013)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hep B	Hepatitis B
Hep C	Hepatitis C
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IP	Investigational Product
IRB	Institutional Review Board
LOCF	Last Observation Carried Forward
MCH/MCHC/ MCV	Mean Corpuscular Hemoglobin/ Hemoglobin Concentration/Volume
MedDRA	Medical Dictionary for Regulatory Activities
MMP	Matrix Metalloproteinase
NCI	National Cancer Institute
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PP	Per Protocol
qPCR	Quantitative Polymerase Chain Reaction
RBC	Red Blood Cell(s)
RCL	Replication-Competent Lentivirus
RDW	Red Cell Distribution Width
SAE	Serious Adverse Event
Sub-I	Sub-Investigator
TEAE	Treatment-Emergent Adverse Events
US/USA	United States of America
WBC	White Blood Cell(s)
WHODrug	World Health Organization Drug Global Dictionary

5. INTRODUCTION

5.1. Background: Localized Scleroderma/Morphea

Localized scleroderma/morphea is an autoimmune inflammatory sclerosing disorder of cutaneous induration that can cause permanent functional disability and disfigurement. This rare fibrosing disorder of the skin and underlying tissues is distinct from systemic sclerosis and encompasses several subtypes classified by the depth and pattern of lesion(s). The underlying pathogenesis of localized scleroderma is not completely understood but is likely multifactorial, involving genetic factors and environmental exposures, culminating in small vessel damage, release of profibrotic cytokines, and ultimately leading to disruption of the balance between collagen synthesis and destruction. The incidence and prevalence of localized scleroderma is poorly described. The incidence of localized scleroderma has been estimated as approximately 0.4 to 2.7 per 100,000 individuals. (Fett, 2011 Part 1; Peterson, 1997). Prevalence of localized scleroderma is approximately 50 per 100,000 individuals (Browning, 2013). The prevalence is similar in children and adults (Peterson, 1997, Leitenberger, 2009).

Overproduction and accumulation of collagen is a hallmark of the disease. Given the increased levels of collagen, a biological approach to break down and inhibit collagen synthesis by a matrix metalloproteinase (MMP) is a novel therapeutic approach for the treatment of localized scleroderma.

The assessment of disease activity and depth of involvement guides therapeutic decision-making in localized scleroderma/morphea. Because of the self-limited nature of localized scleroderma/morphea, patients with limited plaque disease may elect to defer therapy. For patients with superficial (dermal) circumscribed disease who desire treatment, but do not have access to or prefer to avoid the frequent visits required for phototherapy, treatment options include high potency topical corticosteroids, intralesional corticosteroids, a topical vitamin D analog, topical tacrolimus, or imiquimod. For patients with superficial (dermal) forms of morphea who are able to receive phototherapy, treatment with UVA1 is preferred; alternatives include broad-band UVA, narrow-band UVB, or PUVA. Phototherapy is unlikely to be effective for localized scleroderma/morphea involving the subcutaneous tissue, muscle, or bone. Rapidly progressive, severe, disabling disease requires systemic therapy, involving a combination of methotrexate and systemic corticosteroids. Localized scleroderma/morphea may cause joint contractures and other functional impairments secondary to deep tissue sclerosis. All patients should be clinically assessed for the development of these findings. Physical therapy is essential for patients at risk for or who show evidence of functional impairments.

The risk-benefit assessment of pursuing treatment for localized scleroderma lesions depends on the potential for functional impairment and symptom burden due to sclerotic lesions.

5.2. Study Rationale

Fibrocell is developing a two-component therapeutic consisting of FCX-013 and veledimex for the treatment of localized scleroderma (morphea) by resolving fibrotic lesions and normalizing dermal collagen production. The first component, FCX-013, is genetically-modified autologous human dermal fibroblasts that have been engineered with a lentiviral vector to express MMP-1 under the control of a RheoSwitch (RTS®) system. The lentiviral vector-containing gene constructs for MMP-1 and the RTS® is referred to as LV-RTS-MMP-1 (or INXN-2005). The second component, veledimex, is a small molecule which activates the RTS to induce expression of MMP-1. The FCX-013 product is administered by intradermal injection, and veledimex is administered orally in a liquid filled gelatin capsule formulation.

The clinical trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements.

6. TRIAL OBJECTIVES AND ENDPOINTS

Primary Objective

The primary objective of this study is to evaluate the safety of FCX-013 plus veledimex in subjects with moderate to severe localized scleroderma/morphea.

Secondary Objective

The secondary objective of this study is to evaluate the antifibrotic effects of FCX-013 plus veledimex via durometry and the LoSCAT (Localized Scleroderma Assessment Tool).

Safety evaluations include assessment of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs); change in clinical laboratory values; change in vital signs; change in electrocardiograms (ECGs); and incidence of replication-competent lentivirus (RCL) antibodies.

Efficacy endpoints include the change from Baseline in the durometer score and LoSCAT score.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is an open-label, single arm Phase 1/2 study being conducted by Fibrocell to evaluate FCX-013 in subjects with moderate to severe localized scleroderma/morphea. Approximately ten subjects will be enrolled and receive FCX-013.

The study is divided into the following periods: Screening (including Manufacture), Treatment, and Long-Term Follow-Up. The Screening Period consists of entry criteria evaluations, the collection of one set of three 3-4 mm biopsies for the manufacture of FCX-013 product, and the identification of potential target sclerotic lesions. Due to the FCX-013 manufacturing process, the Screening Period is expected to have a duration of approximately 4-6 months; however, this period can be extended to accommodate subject scheduling, variations in manufacturing duration and protocol mandated delays (i.e. pauses due to staggered treatment).

After FCX-013 manufacturing is complete, Fibrocell (the Sponsor) and the Investigator will mutually agree on the planned date for injection of FCX-013.

The Treatment Period will have a 12-week duration. One administration of FCX-013 will consist of a maximum of 4 mL of FCX-013 administered in up to sixteen (16) 0.25 mL intradermal injections. On Day 1, FCX-013 will be intradermally injected, using a retro-tracing technique, into the sclerotic lesion targeted for treatment. On Day 1, following the injection of FCX-013, subjects will initiate a 14-day course of veledimex to be taken orally daily. During the Treatment Period, subjects will be evaluated at Weeks 2, 4, and 12, and have an end-of-treatment visit at Week 12.

Treatment with FCX-013 will be staggered for the first three subjects. Administering FCX-013 following each of the first three subjects requires that the previous subject complete Week 4 evaluations, and that the Investigator(s) must have received approval from the Data Safety Monitoring Board (DSMB).

Safety and clinical efficacy evaluations are conducted throughout the study. Safety will be assessed through adverse events (AEs), physical examinations, vital signs, clinical laboratory evaluations, ECGs and concomitant medications.

The Long-Term Follow-Up period is an approximately 15-year period following End of Treatment in which an examination of injection sites is conducted, and safety is monitored annually, at a minimum.

7.2. Number of Subjects

The enrollment target is approximately 10 subjects.

7.3. Treatment Assignment

This is an open label study. All subjects will receive a combination of FCX-013 plus veledimex.

Upon screening, the subject will be assigned a unique Subject Number. Subjects who are eligible for participation will retain the same Subject Number for the duration of the study. Subjects who

satisfy all the inclusion and none of the exclusion criteria will enter a screening period prior to injection(s) with FCX-013 and veledimex administration.

7.4. Randomization and Blinding

This is an open-label, single-arm study. No randomization or blinding techniques will be utilized.

7.5. Dose Adjustment Criteria

7.5.1. Safety Criteria for Adjustment or Stopping Doses

An objective of this study is to generate a safety profile of FCX-013 plus veledimex in subjects with moderate to severe localized scleroderma/morphea. To minimize risk, cumulative safety data will be reviewed by the Medical Monitor. Events that will result in immediate enrollment discontinuation and treatment discontinuation for all subjects are a positive RCL assay and histologically confirmed cancer in combination with the presence of viral vector in the tumor. In addition, the Medical Monitor may interrupt study dosing and/or study entry at any time if medically indicated.

Occurrence of any of these observations will trigger a temporary suspension of FCX-013 plus veledimex administration pending a safety investigation:

- A treatment emergent SAE or suspected SAE related to FCX- 013, the FCX-013 administration procedure, veledimex administration or any other protocol procedure.
- A positive RCL quantitative polymerase chain reaction (qPCR) assay result. A positive RCL qPCR assay will result in suspension of FCX-013 administration. The result will be confirmed by conducting a biological-based assay. If both assays are positive, FCX-013 administration will be discontinued and no further enrollment into the study will be allowed.
- An autoimmune response determined by the Investigator to be possibly, probably or definitely related to treatment.
- Any systemic infection designated as suspected to be related to FCX-013.
- A treatment emergent uncontrolled bacterial, viral, or fungal infection in a lesion that was administered by investigational product (IP) where product sterility testing results reported post injection were positive for contamination.
- Any subject diagnosed with a histologically proven skin cancer (including sarcomas) will be biopsied and assayed for viral vector by qPCR. A positive result for viral vector will cause product administration to be suspended.
- Abnormal laboratory value(s) or clinically significant change from screening/baseline that pose a risk to safe participation.
- Abnormal test procedure result(s) or clinically significant change from screening/baseline that pose a risk to safe participation (e.g., Grade 2 or above Common Terminology Criteria for Adverse Events/CTCAE criteria (v.4.03) for ECG test).

For subject safety, investigators should continue to follow subjects in accordance with study visits and procedures as outlined in the protocol. An occurrence of any of these safety observations will be shared with all study Investigators, DSMB and the appropriate regulatory authorities. The DSMB will review the results of the safety investigation and may request any additional data needed to assess the safety of restarting product administration. The DSMB will determine if the suspension can be lifted or if the trial will need to terminate based on their review of the safety investigation.

7.5.2. Early Cessation of Study Treatment for an Individual

Subjects may voluntarily stop receiving treatment at any time.

Unless a subject withdraws consent, subjects who voluntarily cease to receive treatment will continue to be followed as per the trial protocol and clinical assessment schedule to ensure that full data are obtained.

The Primary Investigator and/or the Sponsor may decide that early cessation of treatment is warranted for any one of the following reasons:

- Occurrence of AEs that pose a risk to safe participation
- Abnormal laboratory value(s) that pose a risk to safe participation
- Abnormal test procedure result(s) that pose a risk to safe participation
- Unsatisfactory therapeutic effect
- Condition no longer requires treatment
- Pregnancy

Subjects can withdraw from the study for any reason including worsening disease and to receive rescue therapy/standard-of-care treatment for worsening disease.

For subjects who are lost to follow-up, the Investigator should show due diligence by documenting in the source documents the steps taken to contact the subject (e.g., dates of telephone calls, emails).

7.6. Study Termination

Fibrocell reserves the right to terminate the study, according to the study contract. The investigator should notify the Institutional Review Board (IRB) in writing of the trial's completion or early termination and send a copy of the notification to Fibrocell.

7.7. Safety Oversight: Data Safety Monitoring Board

A DSMB will be comprised of two clinicians with expertise in dermatology and/or scleroderma, and a statistician. The DSMB will facilitate the management and identification of potential safety concerns that could affect the safety of study subjects and will evaluate the overall progress of the study through the Treatment Period. To minimize risk, cumulative safety data will be reviewed by the DSMB. Principal investigators (PIs), additional sub-investigators (Sub-Is) and scientific personnel may participate in reviews, as appropriate.

The DSMB has the authority to recommend dose or regimen modifications for safety concerns and will provide recommendations about stopping or continuing the trial. To contribute to enhancing the integrity of the trial, the DSMB may also formulate recommendations relating to the selection/recruitment/retention of subjects, their management, improving adherence to protocol-specified regimens and retention of subjects, and the procedures for data management and quality control.

Details regarding the DSMB, procedures, responsibilities, membership, meeting intervals and data to be evaluated will be further described in the study specific DSMB Charter. A written summary documenting the results and recommendations of each DSMB meeting will be maintained on file with the Sponsor.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

Approximately 10 adult subjects with localized scleroderma/morphea will be enrolled in the study at approximately 2 investigative sites in the US.

Subjects must meet all of the inclusion criteria and none of the exclusion criteria at Screening and Day 1 to be considered eligible for participation in this study.

Protocol violations from inclusion and exclusion criteria are prohibited because ineligible study subjects can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety.

8.1. Subject Inclusion Criteria

A subject must meet all of the following criteria to be eligible for treatment in this study:

1. Subject is an adult, ≥ 18 years of age at Screening, with moderate to severe localized scleroderma/morphea with sclerotic lesions which have been unresponsive to standard of care therapy.
2. Subject has stable control of localized disease (clinically inactive) over the 3 months prior to Screening and through Baseline (Day 1).
3. Subject has not participated in previous clinical research study in the 3 months prior to Screening and through Baseline (Day 1).
4. Subject has provided informed written consent.
5. Female subjects of childbearing potential and male subjects engaging in sexual activity that could lead to pregnancy agree to use of at least one of the following adequate birth control regimens while in the study and for 3 months after study medication (FCX-013 or veledimex) is administered:
    - Male partner with vasectomy
    - Male condom AND partner use of one of the contraceptive options below:
        - Spermicide
        - Intrauterine device or intrauterine system
        - Oral contraceptive, either combined or progestogen alone
        - Contraceptive subdermal implant (e.g., Norplant®)
        - Injectable progestogen (e.g., Depo-Provera®)
        - Contraceptive vaginal ring (e.g., NuvaRing®)
        - Transdermal contraceptive patches (e.g., Ortho Evra®)
    - Subjects of childbearing potential who are abstinent agree to use one of the birth control regimens listed if they initiate sexual activity that could lead to pregnancy during the study.

Periodic abstinence e.g., calendar, ovulation, sympto-thermal, post-ovulation methods and withdrawal are not acceptable methods of contraception.

Non-childbearing potential females are defined as females who are premenarchal, or postmenopausal (12 months with no menstrual period without an alternative medical cause), or who have undergone a hysterectomy, bilateral tubal ligation, bilateral oophorectomy (removal of the ovaries), or hysteroscopic sterilization. Documented verbal history from the subject is acceptable.

6. Subject is, in the opinion of the Investigator, able to understand the study, cooperate with the study procedures and willing to return to the clinic for the required follow-up visits.

8.2. Subject Exclusion Criteria

A subject who meets any of the following criteria will be excluded and considered ineligible for participation in the study:

1. Subject has a clinically significant skin disorder other than localized scleroderma/morphea in the anatomical area (e.g., same arm, same side of abdomen) of interest.
2. Subject has localized scleroderma/morphea with potential target lesions only located on the face or over a joint, or lesions that can be successfully managed with topical medications or phototherapy.
3. Subject has symptoms consistent with systemic scleroderma that have not been stable, or that require treatment that has not been stable for 3 months prior to Screening and through Baseline (Day 1).
4. Subject has been treated with UVA1 phototherapy within 2 months prior to Baseline (Day 1).
5. Subject requires treatment with a non-stable regimen of systemic immunosuppressive therapy, for any medical condition, or plans to initiate such treatment during the study period.
6. Subject requires treatment with a non-stable regimen of physical therapy, for localized scleroderma/morphea, or plans to initiate such treatment during the study period.
7. Subject has any medical instability limiting ability to travel to the investigative center.
8. Subject has clinical signs of infection at (or in close proximity to) the target lesion.
9. Subject has a history of, or current, malignancy at/near site of injection (except basal cell carcinoma or squamous cell carcinoma that have been treated).
10. Subject has a history of, or current, clinically significant liver abnormalities.
11. Subject has a history of, or current, clinically significant cardiac abnormalities, or a significant abnormality on ECG, including a QT interval corrected for heart rate (Fridericia; QTcF interval) of > 450 milliseconds in males and > 470 milliseconds in females.

12. Subject has clinically significant laboratory abnormalities which may affect their ability to safety participate in the study.
13. Subject has active infection with human immunodeficiency virus (HIV) as determined by HIV screening, or hepatitis B (hep B) or hepatitis C (hep C), as determined by hep B surface antigen screening, detection of hep C antibodies, or positive result of hep C polymerase chain reaction (PCR) analysis.
14. Subject has an active drug or alcohol addiction.
15. Subject has any known allergy to any of the constituents of the product.
16. Subject has received an interventional chemical or biological investigational study product for the specific treatment of localized scleroderma in the 3 months prior to Screening and through Baseline (Day 1).
17. Subject is pregnant or nursing or plans to become pregnant or nurse during the study period.

8.3. Subject Withdrawal Criteria

A subject is free to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Investigator or Sponsor may also withdraw the subject at any time in the interest of subject safety or for other reasons. Criteria for withdrawal include:

- Consent is withdrawn
- The subject refuses treatment and/or procedures/observations
- Occurrence of unmanageable AEs, or pregnancy
- For other reasons (e.g., significant protocol violation, non-compliance)

The Sponsor may be contacted if clarification is required.

The primary reason for withdrawal must be recorded on the case report form (CRF). Comments or complaints regarding the withdrawal made by the subject must also be recorded on the CRF. Withdrawal information will be communicated to the DSMB at each meeting. Withdrawal should be discussed with the medical monitor prior to withdrawal when possible. Subjects who wish to discontinue treatment or study procedures after receipt of FCX-013 will be asked to continue in the Long-Term Follow-Up Period.

Subjects who withdraw prior to FCX-013 administration will be considered a screen failure and will be replaced. The Sponsor reserves the right to terminate the study.

Discontinuation of FCX-013 administration does not mean discontinuation from the study. The study assessments and procedures for the visit and subsequent visits should be completed as indicated in the Schedule of Events (Table 4) and reason for discontinuation of FCX-013 administration should be documented in the subject's source documents and CRF.

If a subject discontinues from the study, every effort must be made to perform the study assessments and procedures specified for an Early Termination Visit (Week 12). The primary

reason for subject's withdrawal from the study should be documented in the subject's source documents and CRF.

Subjects who discontinue from the study following IP administration will be asked to participate in the Long-Term Safety Follow-up period.

9. TREATMENT OF SUBJECTS

9.1. Description of Investigational Products

Table 1: Investigational Product

	Investigational Product	
Product Name	FCX-013	Veledimex
Dosage Form	Cell suspension	Capsule
Unit Dose	2 mL (containing approximately 1.2 mL of FCX-013)	40 mg
Route of Administration	Intradermal injection	Oral
Physical Description	Opaque liquid	Liquid filled capsule

9.2. Investigational Product Dosing

FCX-013

Subjects will receive intradermal injections of FCX-013 to treatment lesion(s) in a single treatment session, on Day 1.

Table 2 provides details regarding the number of cells, vials and injections per treatment session.

A treatment session of FCX-013 will consist of a maximum of 4 mL of FCX-013 administered in up to sixteen (16) 0.25 mL intradermal injections. The injections will be administered around the perimeter of the sclerotic target lesion(s), approximately 1 cm apart. The Investigator will attempt to administer the full 4 mL of FCX-013. Additional details of FCX-013 administration can be found in Appendix 2.

Table 2: FCX-013 Cell Count, Vial and Injections per Treatment Session

FCX-013 Cells:	~100 million
Concentration of FCX-013 Suspension:	10 to 30 million cells/mL
# Vials:	Up to 5
Cells per Injection:	6 million
Number of Injections:	Up to 16 (each injection 0.25mL)

Veledimex

Veledimex will be administered once daily, starting on Day 1 following FCX-013 injection. The veledimex dose is 160 mg daily (4 capsules containing 40 mg veledimex each), for 14 days.

Veledimex must be taken with food. Compliance with veledimex administration will be verified at the Week 2 visit, based on subject report and capsule count (accountability).

9.3. Lesion Selection Criteria/Guidelines

Up to three small lesions will be selected for potential treatment from the trunk, breast, forearm, armpit, upper or lower extremities. Lesions on the face and over joints will be excluded. Sclerotic lesions will be chosen which have not responded to standard of care. An area of unaffected skin in the same body area, typically contralateral, will be measured as a control.

Final lesion selection will occur on Day 1, and the total injection area must be approximately 16 linear cm.

9.4. Prior and Concomitant Medications

Subject's prior and concomitant medications/treatments (including over-the-counter or prescription medication, vitamins and/or herbal supplements) and skin care regimen will be reviewed and recorded at Screening and reviewed/updated at every visit. Medications/treatments used within 30 days prior to Baseline (Day 1) will be reported in the database.

Any medications/treatments administered to the subject during the study must be recorded including all anesthesia medication used during biopsy procedures. Any changes in concomitant medication/treatments will also be recorded. If the reason for change is related to an AE, an AE must be recorded.

Throughout the study, any concomitant medications/treatments deemed necessary to provide adequate supportive care may be prescribed. In particular, medication should be considered during and after the FCX-013 injections to treat pain and/or anxiety (e.g., lorazepam).

During long term follow up visits (annually for up to 15 years), concomitant medications should also include discussion of exposure to mutagenic agents and other medicinal products to meet regulatory guidelines.

Skin Care Regimen

There are few restrictions on skin care however, all target wounds should receive same standard of care. CBD oil and steroids should not be used at the target lesions. Routine skin care may continue throughout the study.

Prohibited Medications

The Medical Monitor should be contacted if there are any questions regarding prohibited medications/treatments and nondrug therapies.

The use of the following products is prohibited during this study:

- Other investigational scleroderma medications/treatments or procedures
- CBD oil or steroids as skin treatments at the target lesions

Caution should be used when prescribing medically required medications that are classified as CYP450 3A4 inducers, inhibitors, or substrates. See Table 3 for a list of medicine classes that may affect CYP450 3A4 and cause potential drug-drug interactions with veledimex. If such

medications cannot be avoided or the subject is on stable doses, these subjects should be monitored, and doses adjusted accordingly.
(https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractions labeling/ ucm093664.htm).

Table 3: Medicine Classes that may Affect CYP450 3A4

CYP3A Substrates	CYP3A Inhibitors	CYP3A inducers
Macrolide antibiotics: Clarithromycin, erythromycin, NOT azithromycin, telithromycin Anti-arrhythmics: quinidine→3-OH(not 3A5) Benzodiazepines: Alprazolam, diazepam→3OH, midazolam, triazolam Immune Modulators: Cyclosporine, tacrolimus (FK506), sirolimus HIV Antivirals: Indinavir, ritonavir, saquinavir, nevirapine Prokinetics: cisapride Antihistamines: Astemizole, chlorpheniramine Calcium Channel Blockers: Amlodipine, diltiazem, felodipine, Nifedipine, nisoldipine, nitrendipine, verapamil HMG CoA Reductase Inhibitors: Atorvastatin, lovastatin, NOT pravastatin, NOT rosuvastatin, simvastatin PDE-5 Inhibitors: Sildenafil, tadalafil, vardenafil Others: Alfentanyl, aripiprazole, boceprevir, buspirone, carbamazepine, gleevec, haloperidol, pimozide, quinine, tamoxifen, telaprevir, trazodone, vincristine	HIV Antivirals: indinavir nelfinavir ritonavir clarithromycin itraconazole ketoconazole nefazodone erythromycin grapefruit juice verapamil suboxone diltiazem cimetidine amiodarone NOT azithromycin fluvoxamine troleandomycin voriconazole	carbamazepine efavirenz nevirapine phenobarbital phenytoin pioglitazone rifabutin rifampin St. John's Wort troglitazone

9.5. Contraception

Female subjects of childbearing potential and fertile male subjects who are engaging in sexual activity that could lead to pregnancy must use at least 1 of the following adequate birth control regimens while in the study and for 3 months after study medication (FCX-013 or veledimex) is administered.

- Male partner with vasectomy
- Male condom AND partner use of one of the contraceptive options below:
  - Spermicide
  - Intrauterine device or intrauterine system
  - Oral contraceptive, either combined or progestogen alone
  - Contraceptive subdermal implant (e.g., Norplant®)
  - Injectable progestogen (e.g., Depo-Provera®)
  - Contraceptive vaginal ring (e.g., NuvaRing®)
  - Transdermal contraceptive patches (e.g., Ortho Evra®)
- Subjects of childbearing potential who are abstinent are eligible, but they must agree to use one of the birth control regimens listed above if they begin engaging in sexual activity that could lead to pregnancy during the study.

Periodic abstinence e.g., calendar, ovulation, sympto-thermal, post-ovulation methods and withdrawal are not acceptable methods of contraception.

Non-childbearing potential females are defined as females who are premenarchal, or postmenopausal (12 months with no menstrual period without an alternative medical cause), or who have undergone a hysterectomy, bilateral tubal ligation, bilateral oophorectomy (removal of the ovaries), or hysteroscopic sterilization. Documented verbal history from the subject is acceptable.

10. STUDY ASSESSMENTS AND PROCEDURES

10.1. Schedule of Study Visits and Assessments

The study visit schedule visit windows and assessments and procedures and their associated timings are summarized in the Schedule of Events (Table 4). Every effort should be made to adhere to the study assessments and procedures, visit schedule and visit windows as specified in the Schedule of Events. Visit windows are calculated in relation to Baseline (Day 1).

Additional information about the visits can be found in Section 10.2, and information about specific assessments and procedures can be found in Section 10.3.

Study assessments and procedures will be performed only after signed informed consent is obtained.

Table 4: Schedule of Events

Visit → / Assessment ↓	Screening	Baseline (Day 1)	Week 2 (Day 15, -1/+3 days)	Week 4 (Day 29, ±5 days)	Week 12/ End of Treatment (Day 85, ±5days)	Week 26 (Month 6, ±4 weeks) Week 52 (Year 1, ±4 weeks)	Years 2-15* (52-week intervals, ±8 weeks)
Informed Consent	X						
Eligibility Criteria	X	X					
Demographics	X						
Medical/Surgical History	X	X					
Physical Exam/Vital Signs	X	X*	X	X	X		
Skin Assessments	X	X	X	X	X	X	
Electrocardiogram	X	X	X	X	X		
LoSCAT	X	X		X	X	X	
Durometry		X		X	X	X	
SkinDex		X			X	X	
(3) 3-4 mm biopsies/FCX-013	X						
Inject FCX-013		X					
Dispense/Collect Veledimex		X	X				
Prior/Concomitant Medications	X	X	X	X	X	X[1]	X[1]
Adverse Events	X	X	X	X	X	X[2]	X[2]
Hematology and Chemistry	X	X	X	X	X		
HIV, Hep B, Hep C Testing	X						
Urine Pregnancy Test, if applicable		X	X	X	X		
RCL Assay	X				X	X	X[3]

Table 4: Schedule of Events (Continued)

***include height and weight at Baseline**

An unscheduled visit, with necessary assessment, may occur as needed.

Notes:

a) For any subject who is diagnosed with or dies of a new malignancy, attempts will be made to collect a biopsy of the neoplastic tissue or pertinent autopsy tissue to perform relevant RCL testing.

b) For any subject with a malignant growth in a region of FCX investigational gene therapy administration, attempts will be made to collect a skin biopsy of the malignant tissue for viral vector presence and potentially clonality of vector integration testing, as available.

c) In years 1-5 only, a skin biopsy from the region of FCX investigational gene therapy administration (i.e., treated skin area) may be taken to test for relevant transgene and vector persistence *in subjects who consent to the collection of the biopsies required to perform the assay*. However, collection of biopsies will stop if transgene and vector persistence is undetected.

***Long-term Follow-Up for years 2-15 may be performed by contacting the subject to review/record requested information, ideally scheduled to follow annual visits and assessment (including relevant laboratory analyses) performed by the subject's health care provider.**

1. Report exposure to mutagenic agents and other medicinal products.

2. Report adverse events of special interest and emergence of new clinical conditions, including, but not limited to: new malignancy, new incidence or exacerbation of a pre-existing neurologic disorder, new incidence or exacerbation of a prior rheumatologic or other autoimmune disorder, new incidence of a hematologic disorder, unexpected illnesses and hospitalization(s).

3. Collection and analysis of a blood sample to monitor for RCL may be performed yearly for up to 15 years. If all post-treatment RCL assays are negative through one year following subject's final investigational product administration, collection of the yearly follow-up samples may be discontinued.

10.2. Study Procedures by Visit

Every effort should be made to adhere to the study assessments and procedures as outlined in the Schedule of Events (Table 4).

Supplementary by-visit instructions are presented in this section.

10.2.1. Prescreening and Screening (Visit 1)

Prescreening

An Investigator or designee may prescreen medical histories of potential subjects with localized scleroderma/morphea for potential inclusion into this study in accordance with their IRB's policy on chart reviews. Some activities may include:

- The Investigator may request additional PHI disclosure authorizations from the potential subject to assist with Pre-Screening.
- Potentially eligible subjects may be mailed an IRB-approved information letter which includes a study overview, key inclusion/exclusion criteria, information about the recruitment process, and contact information.

If a potential subject contacts the Investigative Site indicating interest in the study, an Investigator or designee reviews the letter contents with the subject and addresses questions. At this time the Investigator or designee can verbally review the inclusion / exclusion criteria. If the potential subject remains interested in participating in the study, a copy of the informed consent may be sent to the potential subject to review.

Screening

Screening evaluations may be conducted over multiple visits, however, informed consent must be obtained at the first screening visit and collection of biopsies for FCX-013 manufacturing should also be completed at the first screening visit, or as soon as possible thereafter.

Written informed consent must be obtained from the subject prior to performing any study assessment or procedures. Provide subject with a copy of the signed and dated consent form, and document informed consent in the subject's source documents and CRF.

The Investigator will review all screening data when all test results are available. If screening test results received after manufacturing biopsies have been taken show the subject does not meet study criteria, the subject will be withdrawn (screen failure) and all material obtained for manufacturing will be destroyed unless consent has been obtained to use the tissue for future research.

10.2.2. Baseline (Day 1)

Subjects will be reassessed to confirm final eligibility to participate in the study.

Physical and laboratory safety assessments, and the LoSCAT and durometry assessments should be performed, and the SkinDex 29+3 administered, prior to administration of FCX-013.

Post-administration of FCX-013, AEs and concomitant medications should be assessed and recorded, as applicable.

Veledimex should be provided, with instruction to initiate dosing with food that day and then daily for 14 days.

10.2.3. Week 2 (Day 15) / Week 4 (Day 29)

At Week 2, remaining veledimex should be collected, and the subject should be queried about their dosing compliance, including any dates of missed doses, and this information should be recorded.

10.2.4. Week 12/End of Treatment

If a subject discontinues from the study, every effort must be made to perform the End of Treatment study assessments and procedures. The primary reason for subject's withdrawal from the study should be documented in the subject's source documents and CRF.

10.2.5. Long-Term Follow-Up

During the long-term follow-up period, the subject, and/or their healthcare provider will be contacted annually to collect information regarding AEs, health changes and concomitant medications.

Collection and analysis of a blood sample to monitor for RCL may be performed yearly for up to 15 years. If all post-treatment RCL assays are negative through one year following subject's final administration of FCX-013, collection of the yearly follow-up samples may be discontinued.

For any subjects that require tissue biopsies (RCL, insertional mutagenesis, and/or transgene and vector persistence), please contact the sponsor for current procedures.

10.2.6. Unscheduled Visit

An unscheduled visit may occur during the study as necessary based on investigator's judgement. At every unscheduled visit, AEs, health changes, and concomitant medications will be assessed. Additional procedures and assessments may be performed based on investigator's judgment.

10.3. Assessments

10.3.1. Demographics

Subject's demographic information will be collected at the Screening visit and will include initials, date of birth (DOB), sex, and subject-reported race and ethnicity.

10.3.2. Medical/Surgical History, Prior and Concomitant Medications

Medical/surgical history will be collected at the Screening visit to ensure subjects are eligible for participation in the study (per inclusion Section 8.1 and exclusion Section 8.2 criteria).

The Investigator or designee will collect a complete medical history at the Screening visit, including review of subject's prior and concomitant medications (per Section 9.4). The medical history will include review and recording of dermatological (including scleroderma history), neurological, ophthalmic, ear/nose/throat, cardiovascular, respiratory, gastrointestinal,

hematologic, endocrine, renal, hepatic, psychiatric and other conditions/diseases, as well as allergies (drug, food, environmental).

The Investigator or staff must record all clinically or medically relevant information as medical history.

10.3.3. Vital Signs

Vital sign measurements include systolic and diastolic blood pressure, pulse, and respiratory rate as well as temperature. Blood pressure, pulse, and respiratory rate are taken after subjects are in a rested state. Blood pressure determined by cuff (manual or automated) is acceptable although the same method should be used throughout the study. Temperature, oral or tympanic, is acceptable although the same method should be used throughout the study.

10.3.4. Physical Examination

Body systems evaluated will include:

- General appearance (include height and weight at Baseline)
- HEENT (Head, Ears, Eyes, Nose, Throat)
- Spine/Neck/Thyroid
- Respiratory
- Cardiovascular
- Abdomen
- Nervous System
- Musculoskeletal

Abnormalities or changes in severity noted during the exam should be reported in the source document and on the appropriate CRF page. If a new clinically relevant finding occurs (not noted prior to FCX-013 plus veledimex administration), an AE must be recorded. In addition, resolution of any abnormal findings during the study will be noted in the source document and appropriate CRF if clinically significant.

Skin Assessments

A qualified individual will perform a skin examination at all visits to the Investigative Site. If at any point in the study a skin cancer occurs in the region of the FCX-013 administration, attempts will be made to collect samples of the skin cancer to evaluate cells for the presence of viral vector. Biopsy and injection sites will be monitored for appropriate wound healing and adverse reactions.

10.3.5. Electrocardiogram

A 12-lead ECG and rhythm strip measurements will be made with the subject in a supine position having rested in this position for at least 10 minutes before each reading. ECG recordings will be digital, with paper tracings printed at a standard paper speed of 25 mm/sec and gain of 10 mm/mV, with a lead II rhythm strip. Intervals RR, PR, QRS, QT, QTcF, and QTcB

will be calculated automatically and checked by a study physician. Individual ECG tracings will be stored digitally for independent assessment, if necessary.

10.3.6. Skin Biopsy for FCX-013 Manufacturing

Three (3) 3-4 mm skin biopsies for the purpose of FCX-013 manufacturing will be collected at the first Screening visit if at all possible. Biopsies will be collected from subject's normal/unaffected/intact skin with the specific location varying on a case-by-case basis based on the Investigator's judgment (refer to Appendix 1 for additional collection site guidance).

An additional set of skin biopsies may be collected if the manufacturing process does not yield an FCX-013 cell count sufficient for at least one treatment session or does not meet release specifications.

Biopsy collection procedures are provided in Appendix 1. Additional details regarding biopsy supply requisition, scheduling, collection, preparation and shipment of the biopsies to Fibrocell will be detailed in the Study Procedures Manual, as applicable.

10.3.7. Laboratory Assessments: Hematology and Blood Chemistry

Whenever possible, the amount of blood collected should be minimized.

Serum chemistry and hematology laboratory analyses will occur locally. A copy of the reports will be maintained as part of the subject's source documentation.

Reference ranges will be supplied by the laboratory and used to assess the laboratory data for clinical significance and out-of-range pathological changes. Abnormal laboratory values which are unexpected or not explained by the subject's clinical condition should be repeated until confirmed, explained or resolved. Changes from lab results after the Baseline (Day 1) will be recorded as an AE if deemed clinically relevant by the Investigator or medically qualified designee.

The following laboratory evaluations will be conducted as indicated in the Schedule of Events (Table 4):

Serum Chemistry / Metabolic Panel

Albumin	AST (SGOT)	Bilirubin, direct & indirect	Globulin
Alkaline Phosphatase	Urea Nitrogen	CO2	Potassium
Total Anion Gap	Calcium	Creatinine	Sodium
ALT (SGPT)	Chloride	Glucose	Total Protein

Hematology / Complete Blood Count with Differential

Hemoglobin	MCV	Neutrophils, % and absolute count
Hematocrit	MCH	Lymphocytes, % and absolute count
Platelet Count	MCHC	Monocytes, % and absolute count
RBC	WBC	Eosinophils, % and absolute count
RDW		Basophils, % and absolute count

HIV, Hepatitis B, and Hepatitis C Testing

A blood sample for diagnostic screening tests for HIV antibodies, Hepatitis B surface antigen (HBsAg), and Hepatitis C (Hep C) antibody and PCR analysis will be collected at Screening, and the analyses will occur locally.

Pregnancy Screen

A urine pregnancy test will be performed as indicated in the Schedule of Events (Table 4) on all female subjects of childbearing potential (Section Section 9.5). Urine pregnancy testing must be performed locally, prior to FCX-013 administration. In the case of a positive pregnancy test, FCX-013 will not be administered.

Pharmacokinetic Assessments

No pharmacokinetic assessments will be performed in this study.

10.3.8. Replication Competent Lentivirus Analysis

A blood sample for RCL analysis will be collected at the time points indicated in the Schedule of Events (Table 4). A blood sample for RCL analysis is not required at Screening if previously performed within the past 2 years and results are contained in the subject's medical records. If RCL analysis was performed >2 years from Screening, a discussion with the Medical Monitor should occur to determine if the testing timeframe is acceptable. Results must be available and reviewed prior to subject's final eligibility determination on Day 1. If all post-treatment blood RCL assays for an individual subject are negative through one year following the subject's final IP administration, collection of the yearly follow-up sample may be discontinued for that subject.

If any post-treatment samples are positive, the result should be confirmed by conducting a biological-based (direct culture) assay and more extensive subject follow-up will be undertaken in consultation with the Sponsor and Center for Biologics Evaluation and Research (CBER).

During the Long-Term Follow-Up portion of the study (as noted in the Schedule of Events), for any subjects that require RCL analysis of biopsies due to malignancies or other reasons, please contact the sponsor for current procedures.

RCL analysis will occur at an outside lab.

10.3.9. Durometry

A durometer is a handheld device that can measure skin firmness or hardness. Durometric examination will be performed using a thin clear plastic (such as Saran wrap or thin report cover/page divider) to identify at least 3 anatomic markers and alignment around the target lesion(s). The approximate center of the lesion should be identified and marked on this template, and the durometer should be centered over this area, with gentle pressure and complete contact, and a series of at least 3 readings should be obtained and recorded. If there are outlying readings, this should be repeated until 3 readings are reasonably concurrent, and these should be recorded. An average score will be calculated for each target lesion. The template used to identify the lesion and the center for readings should be retained for use at subsequent visits. The template may also be used to mark injection points.

10.3.10. LoSCAT

The Localized Scleroderma Assessment Tool (LoSCAT) (Appendix 3) should be completed by the Investigator to capture disease activity parameters. The LoSCAT is used to classify patients with morphea by disease severity and to identify clinically significant improvement in activity.

Mild, moderate and severe activity corresponds with LoSCAT activity index (LoSAI) scores of 0–4, 5–12 and 13 and over, and with Physician's Global Assessment of activity (PGA -A) scores of 0–10, 11–30 and 31 and over. Mild, moderate and severe damage corresponds with LoSCAT damage index (LoSDI) scores of 0–10, 11–15 and 16 and over, and with PGA of damage (PGA -D) scores of 0–18, 19–30 and 31 and over.(Teske, 2020)

Scores for each site will be based on the most severe score for each parameter.

10.3.11. SkinDex

The SkinDex 29+3 (Appendix 4) is a skin-specific quality of life questionnaire which assesses three subscales: emotions, symptoms, and functioning in the month preceding administration. A fourth subscale was added to characterize morphea-specific concerns: (1) activity limitation as a result of disease, (2) concern for involvement of internal organs and (3) feelings of isolation.(Klimas, 2015)

The SkinDex 29+3 will be administered by providing the questionnaire to the subject, who will be instructed to respond to each question. Study staff will review the questionnaire upon completion and will return it to the subject and ask that they respond to any incomplete lines. The responses will be summed at each applicable timepoint.

11. STUDY DRUG MATERIALS AND MANAGEMENT

11.1. Study Drug Materials and Administration

11.1.1. FCX-013

FCX-013 will be manufactured from one set of three 3-4 mm biopsies obtained at the Screening Visit. Upon receipt of the biopsies at Fibrocell, FCX-013 will be manufactured by gene modification and expansion of dermal fibroblasts obtained from the biopsy. The tissue will be digested with enzymes to release the fibroblasts, which will then be seeded into a tissue culture vessel. The cells will be expanded, transduced with INXN-2005 (a lentiviral vector encoding the functional MMP-1 gene), and expanded further. If the manufacturing process does not yield an FCX-013 cell count sufficient for at least one administration, or does not meet manufacturing release specifications, an additional set of biopsies may be requested from the subject.

This IP will be provided to the Investigative Site as an opaque cell suspension in 2.0 mL cryovials containing approximately 1.2 mL of FCX-013 with a recoverable volume of 1.0 mL per vial.

Packaging and Labeling

Up to five (5) vials of FCX-013 will be provided per subject, per treatment session. The vials will be labeled with a minimum of the subject number and the date of manufacture. The secondary container in which the vials are shipped will include the following information:

- IP Name: FCX-013
- Lot Number
- Fill Date and Time
- Expiration Date and Time
- Nominal Conc./Vol.: 10-30 million cells/mL in 1.0 mL
- Manufactured by Fibrocell Technologies Inc. Exton, PA
- CAUTION: NEW DRUG – Limited by US Federal Law to Investigational Use
- NOT EVALUATED FOR INFECTIOUS SUBSTANCES

The cells will be transported to the investigative site as a suspension and the vial will be packaged in a temperature controlled and monitored shipper and delivered by overnight courier.

Storage

After receipt of the shipped vials, they must be kept sealed in the shipper until ready for use. The Investigator will be responsible for accurate, written records of all FCX-013 received. The Sponsor or designee will be permitted upon request to audit the administration procedures and records.

FCX-013 Drug Product will be shipped same day or overnight delivery to the clinic and must be administered within 40 hours of the fill time as indicated on the label.

Preparation and Administration

One administration of FCX-013 is up to 4 mL of cell suspension administered in up to sixteen (16) 0.25 mL intradermal injections.

The maximum dose of FCX-013 will be determined by characteristics of the lesion(s) chosen. Approximately 100 million cells will be administered at each dose administration. One administration of FCX-013 will consist of a maximum of 4 mL of FCX-013 administered in up to sixteen (16) 0.25 mL intradermal injections. The injections will be administered in and across the sclerotic area of target lesion(s). The Investigator will attempt to administer all 4mL of FCX-013. This will be accomplished by selecting target lesions that are as close as possible to 16 linear cm.

Table 5 provides details regarding the number of cells, vials and injections per administration.

Table 5: FCX-013 Cell Count and Injections per Administration

FCX-013 Cells	**~100 million**
Concentration of FCX-013 Suspension	**10-30 million cells/mL**
# Vials	**Up to 5**
Injections per Vial	**1**
Cells per Injection	**6 million**
Number of Injections	**Up to 16**

11.1.2. Veledimex

The veledimex product is supplied as a 50 mg/g Solutol™ formulation, encapsulated in Licaps® hard gelatin capsules to produce veledimex at a strength of 40 mg per capsule.

Packaging and Labeling

Veledimex Hard Gelatin Capsules, 40 mg (Solutol®)

Study No.: XXXXX Lot No.: XXJM-XXX
Manufacturing Date: DDMMMYYYY
Contains 30 capsules / bottle
Storage Conditions: 15°C - 25°C For Oral Administration Only

Caution: New Drug – Limited by Federal (or United States) Law for Investigational Use Only

Manufactured for Fibrocell Technologies, Inc. by Capsugel® (Now a Lonza Company)
Z.I. de Camagnon BP 320 F-56803 Ploërmel Cedex, France

The manufacturing location may be revised during the course of the study.

Storage

The primary container closure system for veledimex drug product packaged clinical supplies is 75 cc white HDPE, round bottle with 33 mm white child resistant closure.

Veledimex capsules should be stored at room temperature under dry conditions. Intact veledimex capsules can be considered to be nontoxic and can be safely handled without special precautions.

Preparation and Administration

For the current study, veledimex is intended to be administered once daily at a maximum daily dose of 160 mg (4 capsules containing 40 mg veledimex each).

11.2. Study Drug Accountability

An accurate record of all supplies received and used at each site should be maintained and updated regularly.

Subject will be instructed to return all veledimex capsules at specified protocol visits for study treatment inventory and assessment of subject compliance.

The dispensing and return of all veledimex will be recorded on the study Investigational Product Dispensing Record. The Subject Number and the initials and date of the person dispensing and receiving the returned treatment will be documented on this form.

Inventory records must be readily available for inspection by the study monitor and/or auditor, and open to inspection by regulatory authorities at any time.

11.3. Study Drug Handling and Disposal

After receipt of the shipped vials, they must be kept sealed in the shipper until ready for use. The Investigator will be responsible for accurate, written records of all FCX-013 received. The Sponsor or designee will be permitted upon request to audit the administration procedures and records.

FCX-013 Drug Product will be shipped same day or overnight delivery to the clinic and must be administered within 40 hours of the fill time as indicated on the label.

12. ADVERSE EVENTS

Adverse events will be collected from the time the subject signs the informed consent form (ICF) until the final visit/contact with the subject.

At each visit/contact, the Investigator or designee is responsible for reviewing, documenting, and reporting events that meet the definition of an AE.

Subjects should be asked a non-leading question in order to avoid bias in eliciting AEs, such as "Have you had any changes in your health since your last visit?" at each visit/contact. It is important to question the subject in a non-leading way about changes in their health or concomitant medication usage since their last visit.

* For any subject who develops an AE suggestive of a retrovirus-associated disease after FCX-013 treatment, attempts will be made to collect any relevant clinical samples for available RCL testing

*For any subject who dies or is diagnosed with a neoplasm after FCX-013 treatment, attempts will be made to collect a biopsy of the neoplastic tissue or pertinent autopsy tissue to assay for available RCL testing by qPCR.

Following the subject's initial report of an AE, the Investigator or designee is required to proactively follow-up with the subject regarding any previous AE that hasn't resolved at subsequent visits/contacts.

12.1. Adverse Event Definitions

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, disease or exacerbation of a pre-existing condition temporally associated with the use of a medicinal (investigational) product.

Signs and/or symptoms of the disease under study/lack of efficacy should not be considered as AEs, as long as they are within the normal day-to-day fluctuation or expected progression of the disease. However, significant worsening (e.g., increase in severity or frequency) of the signs and/or symptoms should be recorded as an AE. Any clinically significant change from Screening, based upon the opinion of the Investigator, in physical or examination findings and/or vital signs should be recorded as an AE.

A change in the value of a safety laboratory evaluation can represent an AE if the change is clinically significant, based upon the opinion of the Investigator, or if, during treatment with the IP, a shift of a parameter is observed from a normal value to a pathological value, or a further worsening of an already pathological value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the IP, and the range of variation of the respective parameter within its reference range, should be taken into consideration. The Investigator should decide, based on the above criteria and the clinical condition of the subject, whether a change in a laboratory parameter represents an AE. For pathological laboratory values that were not present prior to IP administration, follow-up laboratory evaluations should be performed until the values return to within reference range or until a plausible explanation is found.

Any AE occurring after administration of IP will be considered a TEAE.

Examples of events meeting the definition of an AE **include**:

- Any abnormal laboratory test results (hematology, chemistry) or other safety assessments (e.g., physical examination, vital signs measurements), including those that worsen from Screening, and felt to be clinically significant based upon the medical and scientific judgment of the Investigator;
- Exacerbation of a chronic or intermittent pre-existing condition (e.g., asthma) including either an increase in frequency and/or intensity/severity of the condition;
- New conditions detected or diagnosed after Screening.

Examples of events that **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition (e.g., anemia);
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition or if these events meet the criteria as SAEs or leads to discontinuation of FCX-013 or from the study;
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE;
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.1.1. Serious Adverse Event

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
  - An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death)
- Inpatient hospitalization or prolongation of existing hospitalization
  - Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- Any event that does not exactly meet this definition yet, in the investigator's opinion represents a significant hazard can be assigned the "important medical events" regulatory reporting serious criteria.

12.2. Reporting Procedure

All AEs observed by the Investigator or site staff or reported by the subject or their caregiver (whether or not attributed to IP), must be fully and completely documented in the subject's source documents and CRF. In the event a subject is withdrawn from the study because of an AE, the primary reason for withdrawal (i.e., due to an AE) must be recorded on the CRF as such.

Each AE requires a complete description including event description (where possible, a diagnosis or if a diagnosis has not been made, individually listed sign(s)/symptom(s)), date of onset and resolution, if applicable, outcome (refer to Section 12.2.2), and actions taken to be recorded in the source documents. The Investigator must also assign the following attributes for each AE: its relationship to the IP (refer to Section 12.2.3) and severity of the AE (refer to Section 12.2.4). The Investigator may be asked to provide follow-up information.

12.2.1. SAE Reporting Procedure

The Investigator or designee must report any SAE to the Sponsor or its designee immediately (within 24 hours (1 working day)) following becoming aware of the event even if the SAE does not appear to be related to IP. This timeframe also applies to becoming aware of additional new information (follow-up) on previously reported SAEs.

Do not delay reporting a suspected SAE in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report. Prompt notification of SAEs by the Investigator to the Sponsor is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

If the subject was permanently withdrawn from the study due to the SAE, this information must be reported in either the initial or follow-up SAE report, and in the End of Study CRF.

For any deaths reported, available autopsy reports and relevant medical reports should be provided with the SAE report.

Specific details regarding the applicable forms, process and contacts for SAE reporting will be provided in the Study Procedures Manual.

The Investigator or designee should notify the IRB of SAEs occurring at the site and other SAE reports received from the Sponsor or its designee, in accordance with IRB procedures. The Sponsor will be responsible for notifying the relevant authorities of any SAE according to applicable regulations.

12.2.2. Follow-Up of Adverse Events

Following the subject's initial report of an AE, the Investigator or designee is required to proactively follow-up with the subject regarding any previous AE that hasn't resolved at subsequent visits/contacts.

Where possible, all AEs should be followed to resolution. Medically significant AEs considered related to the IP by the Investigator or the Sponsor will be followed until resolved or considered stable. Medical tests and examinations will be performed, as appropriate, to document resolution.

All SAEs will be followed until the Sponsor agrees that the event is satisfactorily resolved or that no further follow-up is required.

The Investigator will assess the outcome of each AE using the following criteria:

- **Recovered/Resolved:** The event has improved or subject recuperated.
- **Recovered/Resolved with sequelae**: The subject has recuperated but retained pathological conditions resulting from the prior disease or injury.
- **Recovering/Resolving**: The event is improving.
- **Not recovered/Not resolved**: The event has not improved, or subject has not recuperated.
- **Unknown**: The outcome of the event is not known, not observed, not recorded, or refused.
- **Fatal:** Termination of life as an outcome of the AE.

12.2.3. Relationship of Adverse Event to Investigational Product

The relationship of an AE to IP is to be assessed by the PI using good clinical judgement and according to the following definitions:

- Not Related – no temporal association or the cause of the event has been identified, or the drug cannot be implicated based upon available information.
- Possibly Related – temporal association, but other etiologies are likely to be the cause. However, involvement of the drug cannot be excluded, based upon available information.
- Definitely Related – established temporal or other association (e.g., re-challenge) and event is not reasonably explained by the subject's known clinical state or any other factor, based on available information.

12.2.4. Severity of Adverse Event

The Investigator will make an assessment of the severity of each AE and SAE according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v. 5.0, 2017.

For terms not specified in the CTCAE, the criteria in Table 6 should be used to determine the grade severity.

Table 6: Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the NCI CTCAE Criteria

Grade	Criteria
1	Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living[a]
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living[b]
4	Life threatening consequences; urgent intervention indicated
5	Death related to adverse event

CTCAE = Common Terminology Criteria for Adverse Events.

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

12.3. Pregnancy

Should a pregnancy occur, it must be reported and recorded on Fibrocell's pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

13. STATISTICS

Pre-designed CRFs will be used to collect data for analyses. A clinical database will be managed by a sponsor's representative for this study. The database will be constructed based on the CRF data entry plus laboratory data information. Data queries will be generated and resolved. In addition, range checks of the CRF fields, plausibility and consistency checks across CRF pages will be performed to assess consistency, accuracy and completeness of the data collected and entered into the CRF. Standard SAS datasets will be generated and provided for analysis.

13.1. Sample Size Determination

Since this is primarily a safety study, no formal sample size determination is or was made.

13.2. Analysis Populations

Full Analysis Set

The primary population for analysis of efficacy is the full analysis set (FAS). The FAS population includes subjects who were administered FCX-013.

Per-Protocol

The per-protocol (PP) population is defined as all subjects in the FAS who complete the Week 12 assessments within the specified visit windows, and who do not meet any of the following criteria:

- Did not receive intradermal injections of FCX-013 in the treated lesion(s);
- Did not receive at least 10 doses of veledimex within 15 days of administration of FCX-013;
- Other significant protocol violations, including medically significant violations of inclusion/exclusion criteria or prohibited medications/treatments which may reasonably affect clinical assessments.

Safety

The safety population includes subjects who were administered FCX-013.

13.3. Demographic and Baseline Characteristics

The descriptive summaries of subjects' demographic and baseline characteristics will be presented. A detailed description of subject disposition will be provided.

Subject characteristics will include a summary of the following:

Subject demographics.

Baseline disease characteristics as determined at screening. Pre-existing medical conditions.

Continuous variables will be summarized using number of observations, mean and standard deviation, median and minimum and maximum values. Categorical values will be summarized using number of observations and percentages.

13.4. Safety Analyses

Subject demographics and relevant baseline data will be listed and described. Inclusion and exclusion criteria ensure that participants are suitable for the study. Premature termination will be described.

Physical examinations, vital signs, ECG data, concomitant medications, and laboratory results, including RCL analyses will be listed, and relevant changes will be described by subject and overall, as applicable.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) AE dictionary. Adverse events will be grouped into pre-treatment AEs and TEAEs and will be described by preferred terminology and by body system. The number of adverse event entries, as well as the number of subjects will be described, including by AE type, relationship to FCX-013 plus veledimex, seriousness, and severity of AEs.

13.5. Efficacy Analyses

All subjects who were administered FCX-013 and had at least one assessment of the target lesion post-administration will be included in the efficacy population.

The change from baseline in the LoSCAT and durometry scores (average score at each applicable timepoint) will be reported descriptively, as will changes in the SkinDex 29+3 scores. The primary method of handling data will be last observation carried forward (LOCF).

13.6. Interim Analysis

There will be no formal interim analysis.

13.7. Handling of Missing and Incomplete Data

For efficacy evaluation, the treatment endpoint will be defined as one assessment time point, which includes the last measurement obtained during the study for a variable. No other imputation of values for missing data will be performed. Standard clinical monitoring and data management practices will be used to ensure the integrity of data.

14. ETHICS AND GENERAL STUDY CONDUCT CONSIDERATIONS

14.1. Ethical Conduct of the Study

The Investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. As this study is conducted under a US Investigational New Drug application (IND), the Investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50 and 21 CFR, part 56 are adhered to.

Since this is a "covered" clinical trial, the Investigator will ensure that 21 CFR, part 54 is adhered to. This requires that the PI and all Sub-Is must provide documentation of their financial interest or arrangements with the Sponsor, or proprietary interests in the IP being studied. This documentation must be provided before participation of the PI and any Sub-I. The PI and Sub-Is agree to promptly notify the Sponsor or its designee if any relevant changes occur during the course of the study and for 1 year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol-defined activities.

14.2. Institutional Review Board

This study will be conducted in full compliance with the United States (US) CFR for IRBs 21 CFR, part 56. Before enrollment of subjects into the study, this protocol and any material to be provided to or seen by the subject (e.g., subject information letters, informed consent/assent forms, descriptions of the study used to obtain informed consent/assent, advertising material) will be submitted to an appropriate IRB for review and approval. Approval from the IRB must be obtained before starting the study and should be documented in a letter to the Investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval. IRB approvals must be sent to the Sponsor or its designee before initiation of the study.

Any amendments or modifications made to the protocol or any accompanying material to be provided to the subject after receipt of IRB approval must also be submitted to the IRB for review and approval before implementation.

The Investigator, or designee, will be responsible for obtaining IRB approval/renewal throughout the duration of the study at the frequency specified by the IRB. Copies of the investigator's reports and the IRB written continuance of approval must be sent to the Sponsor or its designee.

The Investigator, or designee, should notify the IRB of important deviations from the protocol and any SAEs occurring at the site or other SAE reports received from the Sponsor or its designee, in accordance with IRB procedures.

All correspondence with the IRB must be retained in the study regulatory files.

14.3. Subject Information and Consent

14.3.1. General Provisions

Informed consent is a process that is initiated prior to the subject's agreement to participate in the study and continues throughout the subject's study participation.

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US CFR for Protection of Human Subjects 21 CFR, part 50, subpart B (§50.20, §50.25, §50.27), subpart D as applicable, the Health Insurance Portability and Accountability Act (HIPAA), if applicable), and local regulations.

The Investigator or designee will prepare an ICF and HIPAA authorization, as applicable and provide the documents to the Sponsor or its designee for approval prior to submission to the IRB. The ICF must contain the basic required elements of consent and additional elements, as applicable, as specified in 21 CFR subpart B §50.25 and will also comply with local regulations. Agreement from the Sponsor or its designee must also be obtained for all changes to the ICF.

The Investigator or designee is responsible for obtaining written informed consent/assent from the subject or legally authorized representative (see note below) before any protocol-specific procedures are performed. Informed consent/ will be obtained after a full explanation of the purpose of the study, risks and discomforts involved, potential benefits, etc. have been provided in both oral and written form. The subject be given ample opportunity to inquire about details of the study. The ICF that is used must be the current IRB approved version and must be signed and personally dated by the subject and by the person who obtained the consent (not necessarily an investigator).

> NOTE: A legally authorized representative is an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

If a potential subject is illiterate or visually impaired and does not have a legally authorized representative, the Investigator or designee must provide an impartial witness to read the informed consent form to the subject. Thereafter, both the subject and the impartial witness must sign the informed consent form to attest that informed consent was freely given and understood.

The acquisition of informed consent should be documented in the subject's medical records. A copy of the signed consent form must be provided to the subject and the original will be maintained with the subject's records.

It is the responsibility of the PI to ensure that any individual delegated the responsibility for obtaining consent are familiar with and adhere to the applicable consent/assent requirements.

14.4. Protocol Compliance

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

14.5. Changes to the Protocol

Protocol modifications or amendments, except those intended to reduce immediate risk to study subjects, may be made only by the Sponsor. IRB approval must be obtained before changes can be implemented. The Investigator or designee must send a copy of the IRB protocol amendment approval letter to the Sponsor or its designee.

Emergency departures from the protocol that eliminate an apparent immediate safety hazard to a particular subject and that are deemed by the Investigator as crucial for the safety and wellbeing of that subject may be instituted for that subject only and documented as a deviation. The Investigator will contact the Medical Monitor as soon as possible regarding such a deviation. These departures do not require preapproval by the IRB; however, the IRB and Medical Monitor must be notified in writing as soon as possible in accordance with the IRB policies after the departure has been made.

14.6. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins as required. Results will be posted as required.

14.7. Study Documentation

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

14.7.1. Investigator Study File

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, in a complete, accurate, and legible manner, suitable for inspection at any time by representatives from the Sponsor, companies that work for and with the Sponsor, applicable regulatory agency(ies), and/or the IRB.

Investigator Study File elements should include, but are not limited to, the following:

- Subject files containing completed CRFs, informed consents/assents, and source documentation.
- Study files containing the protocol with all amendments, investigator's brochure, copies of pre-study documentation along with any updates, all correspondence to and from the IRB (submissions and approvals), Study Procedures Manual, CRF Completion Guidelines, study logs (e.g., subject identification, screening, delegation, site visit), deviations, biological sample records, SAE and IND safety reports / Safety Alert Letters and relevant correspondence with the Sponsor and/or its designee.
- IP accountability (e.g., receipt, dispensing, administration, return/destruction) records and all IP-related correspondence.

14.7.1.1. Subject's Source Documentation

The Investigator must maintain detailed and accurate records (other than the CRF) on all study subjects. The subject's source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to the original

signed/dated informed consent/assent, HIPAA authorization, hospital records, clinical and office charts, laboratory/diagnostic testing results, pharmacy/drug accountability records, diaries, microfiches, radiographs, photographs and correspondence. Telephone conversations with the subject, subject's legal authorized representative and/or the Sponsor or its designee concerning the subject must also be recorded and retained.

14.7.1.2. Pre-Study Documentation Requirements

The Investigator or designee is responsible for providing the following documentation to the Sponsor or its designee for review prior to study enrollment. Any updates of the documentation must also be provided, as applicable, during the conduct of the study.

- Signed and dated investigator's brochure (IB) receipt form
- Signed and dated protocol signature page (Investigator's Agreement)
- A blank copy of the IRB-approved informed consent form (and assent documents, if applicable)
- Copy of the IRB approval of the protocol, information letter, consent form, and assent form, as applicable
- Completed Food and Drug Administration (FDA) Form 1572. Local laboratories, laboratories providing endpoint data and any central laboratories for the study must be listed on the form.
- Up-to-date curriculum vitae or equivalent for each person listed on the Form FDA 1572
- Signed Financial Disclosure Form for each person listed on the Form FDA 1572
- IRB membership list
- The IRB composition and/or written statement that IRB is in compliance with regulations
- Local laboratory(ies) normal ranges
- Documentation of the local laboratory(ies) certification/licenses (e.g., CAP/CLIA or other) or equivalent
- A fully executed Clinical Trial Agreement

14.8. Data Collection, Management, Monitoring, and Retention

14.8.1. Data Collection and Management

For this study, subject data will be entered into the Sponsor-defined CRFs and combined with data provided from other sources, as applicable, in a validated data system. Data will be appropriately documented in the subject's source documents and entered into the CRF when the information is available. Applicable data from the subject's source documents should be recorded in the CRFs completely and promptly. Completed CRFs should be ready for review by the Sponsor or its designee within one (1) week of each study visit for any given subject.

Management of clinical data will be performed in accordance with applicable Sponsor's or its designee's standards and data cleaning procedures will be used to ensure the integrity of the data, e.g., errors will be corrected, and inconsistencies queried in the data.

Adverse events and relevant medical history will be coded using MedDRA. Concomitant medications will be coded using the World Health Organization Drug Global Dictionary (WHODrug Global).

Corrections of data entered into the CRF must be made on the CRF or in the system for electronic CRF and supported by source documents, as appropriate. Corrections to the eCRF through queries and comments will be tracked by the eCRF internal audit trail.

The Investigator is responsible for all information collected on study subjects enrolled in this study. The data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. After a full review of the CRFs by the Sponsor or its designee and resolution of any data clarifications, the Investigator will review, sign, and approve the subject's CRF.

If an electronic CRF is utilized, copies of the final completed CRFs will be provided on a data storage device (e.g., USB flash drive) for archiving at the investigative site following database lock and at or prior to study closure.

14.8.1.1. Subject Confidentiality

The investigator must take all reasonable measures to ensure that the subject's confidentiality is maintained. Study subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor or its designee. On the CRFs or other documents submitted to the Sponsor and those working with the Sponsor, subjects should be identified by their initials, date of birth as applicable, site number, study subject number, and/or unique clinical identification number as applicable only. The Investigator must keep a log showing study subject numbers, names, and addresses for all subjects enrolled in the trial. Documents that are not for submission to the Sponsor or those working with the Sponsor should be kept in strict confidence by the Investigator.

In compliance with Federal regulations/ICH GCP Guidelines, the Investigator and Institution shall permit authorized representatives of the Sponsor and companies that work with the Sponsor, regulatory agency(ies), and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the subject to permit such named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

14.8.1.2. Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries may be entered, tracked, and resolved through the electronic data capture (EDC) system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

14.8.1.3. Monitoring/Auditing

Representatives of the Sponsor, following ICH Guidelines for GCP (E6), will monitor the conduct of this study at regular intervals to verify adherence to the protocol; completeness, accuracy, and consistency of the data entered into the CRFs; and adherence to Federal and local regulations on the conduct of clinical research. In addition, audits or inspections may be carried out by the Sponsor's or its designee's independent Quality Assurance Department, the FDA, local regulatory authority or the IRB. In accordance with ICH Guidelines for GCP, the Investigator must provide direct access to all study records including subject's source data/documents (e.g., subject's medical records), CRFs, and other study related documents (e.g., Investigator Study File, IP drug accountability records). In addition, the Investigator agrees to provide to representatives of the Sponsor, regulatory agency or IRB access to facilities and personnel necessary for the effective conduct of any inspection or audit.

To ensure compliance with GCPs and all applicable regulatory requirements, authorized representatives of the Sponsor may conduct a quality assurance audit. The purpose of a Sponsor audit is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol and any supporting documentation, ICH Guidelines for GCP, and any applicable regulatory requirements.

The Investigator agrees to cooperate with the Sponsor's representatives to ensure that any problems detected in the course of monitoring and/or audit visits, including delays in completing CRFs, are resolved in a timely manner.

In addition, authorized representatives of regulatory agency(ies) and/or an IRB may visit the site to perform audits or inspections. If the Investigator is notified of an inspection by a regulatory authority the Investigator agrees to notify the Sponsor immediately.

14.8.1.4. Retention of Records

All study documents (e.g., subject files, signed informed consent forms, copies of CRFs, Investigator Study File notebook, etc.) must be kept secure and retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., USA, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the Sponsor.

The Investigator must notify and receive prior written consent of the Sponsor before any study documents are destroyed, moved to another location, or assigned to another party.

14.9. Future Use of Stored Specimens and Data

Biopsy specimens and manufactured drug substance may be stored for future manufacturing of Drug Product (FCX-013) for use by the subject in future clinical trials or following FCX-013 commercialization, if applicable.

With the subject's approval, biopsy specimens and fibroblasts obtained for the manufacture of FCX-013 may be stored in a cell bank and be available for research, including manufacturing

process development research, genetic analysis, preclinical or clinical comparison experiments for any cell-based gene-therapy where production of MMP1 may be beneficial. Samples retained for additional future research will be de-identified. Only employees of Fibrocell and/or agents contracted by Fibrocell for the purpose of conducting the research, will have access to the samples and data. However, Fibrocell may contract with secondary experts or laboratories to conduct additional research.

14.10. Publication Policy

The information provided in support of or generated as a result of this study is confidential. Any use or reproduction thereof, including but not limited to publications or presentations by the Investigator or his/her associates, must be submitted to the Sponsor for review and approval prior to publication or presentation in any form. All publications must acknowledge the sponsorship.

15. REFERENCES

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Leitenberger J.J., Cayce R.L., Haley R.W., Adams-Huet B., Bergstresser P.R., Jacobe H.T. (2009). Distinct autoimmune syndromes in morphea: a review of 245 adult and pediatric cases. Arch Dermatol 145(5):545-50.

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APPENDIX 1. BIOSPY COLLECTION PROCEDURES

Manufacturing Biopsies

Biopsies for the purpose of manufacturing are to be obtained from normal or unaffected skin with the specific location varying on a case-by-case basis according to the judgment of the Investigator. Recommended sites for biopsy include the hip, abdomen, back and/or limbs excluding hands/feet, joints, and face. Obtain manufacturing biopsies after all screening assessments have been completed and subject is deemed eligible to participate in the study. Three 3-4 mm biopsies will be obtained for FCX-013 manufacturing purposes. Additional sets of biopsies may be collected if the manufacturing process does not yield an FCX-013 cell count sufficient for one administration or do not meet release specifications.

All medications used must be recorded in the subject's source documents and CRF.

Collection Procedures

1. Anesthetize the area by topical anesthetic, local perfusion.
2. Prepare the area.
3. Excise a sample of tissue using the appropriate supplied biopsy punch. The use of forceps and a scalpel may be necessary to remove the biopsy from its base.
4. Gently place excised tissue into cryovial using forceps.
5. Close donor site as appropriate.
6. Complete the appropriate forms, as applicable, with subject information.
7. Package and ship biopsy as described in the Study Procedures Manual, as applicable.

APPENDIX 2. INVESTIGATIONAL PRODUCT ADMINISTRATION INSTRUCTIONS

1. The FCX-013 injections are to be administered by the PI or an appropriately trained, qualified, and delegated Sub-I.
2. Administer anesthesia. Subjects will be administered anesthesia per standard of care at the Investigative Site. To minimize pain and discomfort during the IP administration, the PI or delegated sub-I should determine the most appropriate anesthetic for each subject, including the use of topical anesthetic cream, local anesthesia, conscious (moderate) sedation, or a combination thereof. In addition, medication could be considered during and after the injections to treat pain and/or anxiety (e.g., lorazepam).
3. Mark the lesional skin to indicate injection points, approximately 1 cm apart, around the perimeter of the lesion and across the fibrotic area.
4. Approximately 15 minutes prior to the administration of FCX-013, remove the subject's treatment vials from the shipper.
5. Resuspend the cells by gently inverting the injection vial three times.
6. Tap the top of each vial to release any fluid in the cap prior to opening the vials. Do not dilute the product.
7. Unscrew the cap and, using a detachable bore (21-gauge needle), aseptically draw 1.0 mL from one vial.
8. Once the product is in the syringe, remove the 21-gauge needle and replace it with a larger-gauge needle for injection of the product (e.g. – 25 or 27 gauge). Do not use a 21-gauge needle for injection of the product. Follow sterile technique during this process. Note: Living cells are fragile and should be handled gently, especially when being aspirated into a syringe. Go slowly and use care during this process.
9. Hold the syringe using the proper technique: the bevel facing upwards and the arms of the syringe are vertical. Some clinicians may prefer to bend the needle upwards at about a 15-degree angle to facilitate staying in a superficial plane — but use of this technique is optional. Grip the syringe with the middle and index finger below the arms, placing the thumb on the upper arm. Do not place the thumb on the plunger while directing the needle into the skin to avoid premature discharge of the product.
10. Insert the 25 or 27-gauge needle at the first mark, into or beneath the dermis, at the fibrotic area. The graduated markings on the syringe should be visible to ensure that the correct amount is being injected.
11. Slowly inject FCX-013 0.25 mL per linear centimeter, with light pressure on the plunger, injecting very tiny boluses (the cells must be injected as delicately as possible) into the treatment area as the needle is withdrawn (retro-tracing). The injections should be performed intradermally, at the perimeter of the lesion and across and into the fibrotic area. Stop injecting before withdrawing the needle and remove your thumb from the plunger.
12. Record any seepage of product or other issues or notes regarding the procedure.

APPENDIX 3. LOCAL SCLERODERMA CUTANEOUS ASSESSMENT TOOL (LOSCAT)

LoSCAT Localized Scleroderma Cutaneous Assessment Tool		LoSAI (Localized Scleroderma Skin **Activity** Index)			LoSDI (Localized Scleroderma Skin **Damage** Index)			
		New/Enlarged (past month) 0 = none 3 = N / E	Erythema 0 = none 1 = pink 2 = red 3 = dark red /violaceous	Induration (skin swelling at EDGE) 0 = none 1 = mild 2 = moderate 3 = marked	Dermal atrophy 0 = none 1 = shiny 2 = visible vessels 3 = cliff drop	Sub Q / Deep atrophy 0 = none 1 = flat 2 = concave 3 = marked	Dyspigmentation (hyper or hypo) 0 = none 1 = mild 2 = moderate 3 = marked	Skin Thickness (at CENTER) 0 = none 1 = mild 2 = moderate 3 = marked
	Scalp/Face							
	Neck							
	Chest							
	Abdomen							
	Upper Back							
	Lower Back							
TR	Arm							
TR	Forearm							
TR	Hand							
TR	Thigh							
TR	Leg							
TR	Foot							
TL	Arm							
TL	Forearm							
TL	Hand							
TL	Thigh							
TL	Leg							
TL	Foot							

LoSAI _____ **LoSDI**_____

PGA-A (Physician Global Assessment of Disease Activity)

(0=inactive) (100=markedly active)

PGA-D (Physician Global Assessment of Disease Damage)

(0=no damage) (100=markedly damaged)

APPENDIX 4. PATIENT REPORTED OUTCOME: SKINDEX 29+3

HOW OFTEN DURING THE **PAST MONTH** DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
1. My skin hurts	☐1	☐2	☐3	☐4	☐5
2. My skin condition affects how well I sleep	☐1	☐2	☐3	☐4	☐5
3. I worry that my skin condition may be serious	☐1	☐2	☐3	☐4	☐5
4. My skin condition makes it hard to work or do hobbies	☐1	☐2	☐3	☐4	☐5
5. My skin condition affects my social life	☐1	☐2	☐3	☐4	☐5
6. My skin condition makes me feel depressed	☐1	☐2	☐3	☐4	☐5
7. My skin condition burns or stings	☐1	☐2	☐3	☐4	☐5
8. I tend to stay at home because of my skin condition	☐1	☐2	☐3	☐4	☐5
9. I worry about getting scars from my skin condition	☐1	☐2	☐3	☐4	☐5
10. My skin itches	☐1	☐2	☐3	☐4	☐5
11. My skin condition affects how close I can be with those I love	☐1	☐2	☐3	☐4	☐5
12. I am ashamed of my skin condition	☐1	☐2	☐3	☐4	☐5
13. I worry that my skin condition may get worse	☐1	☐2	☐3	☐4	☐5
14. I tend to do things by myself because of my skin condition	☐1	☐2	☐3	☐4	☐5
15. I am angry about my skin condition	☐1	☐2	☐3	☐4	☐5
16. Water bothers my skin condition (bathing, washing hands)	☐1	☐2	☐3	☐4	☐5
17. My skin condition makes showing affection difficult	☐1	☐2	☐3	☐4	☐5
18. I worry about side-effects from skin medications / treatments	☐1	☐2	☐3	☐4	☐5
19. My skin is irritated	☐1	☐2	☐3	☐4	☐5
20. My skin condition affects my interactions with others	☐1	☐2	☐3	☐4	☐5
21. I am embarrassed by my skin condition	☐1	☐2	☐3	☐4	☐5
22. My skin condition is a problem for the people I love	☐1	☐2	☐3	☐4	☐5
23. I am frustrated by my skin condition	☐1	☐2	☐3	☐4	☐5
24. My skin is sensitive	☐1	☐2	☐3	☐4	☐5
25. My skin condition affects my desire to be with people	☐1	☐2	☐3	☐4	☐5
26. I am humiliated by my skin condition	☐1	☐2	☐3	☐4	☐5
27. My skin condition bleeds	☐1	☐2	☐3	☐4	☐5
28. I am annoyed by my skin condition	☐1	☐2	☐3	☐4	☐5
29. My skin condition interferes with my sex life	☐1	☐2	☐3	☐4	☐5
30. My skin condition makes me tired	☐1	☐2	☐3	☐4	☐5
31. My skin condition causes skin tightness, weakness, and/or joint pain that limits my normal activities	☐1	☐2	☐3	☐4	☐5
32. I worry that my skin condition may affect my internal organs	☐1	☐2	☐3	☐4	☐5
33. I feel lonely because others don't understand what it is like to have my skin condition	☐1	☐2	☐3	☐4	☐5