FI-EB-001

Fibrocell RDEB Phase I/II Protocol

A Phase I/II Study of FCX-007 (Genetically-Modified Autologous Human Dermal Fibroblasts) for Recessive Dystrophic Epidermolysis Bullosa (RDEB)

Status:	**Final**
Protocol Version:	**Version 8.0, 29 Oct 2019**
IND Number:	**16582**
Investigational Product:	**FCX-007**
Phase of Development:	**Phase I/II**

Protocol Signature Page

Sponsor Approval

This protocol has been approved by Fibrocell Technologies Inc. (Fibrocell).

Sponsor Approver: [redacted]

Vice President, Research and Development
Fibrocell Technologies
405 Eagleview Blvd
Exton, PA 19341

[redacted]

Signature

10/29/2019

Date

Principal Investigator's Agreement

I have read Fibrocell's RDEB Phase I/II Protocol:

FI-EB-001: A Phase I/II Study of FCX-007 (Genetically-Modified Autologous Human Dermal Fibroblasts) for Recessive Dystrophic Epidermolysis Bullosa (RDEB)

I have fully discussed the objectives of this trial and the contents of this protocol with the Sponsor's representative.

I agree to conduct the study as outlined herein and in accordance with International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP), with applicable Food and Drug Administration (FDA) regulations set forth in 21 CFR Parts 50,54, and 312, and all other applicable regulatory requirements.

Principal Investigator Name: _____

_____

Signature

_____

Date

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Abbreviations

AEs ..... adverse events
ALT (SGPT) ..... alanine aminotransferase, included in metabolic panel
AST (SGOT) ..... aspartate aminotransferase, included in metabolic panel
BMZ ..... basement membrane zone
BP ..... base pair
C7 ..... type VII collagen
CBC ..... complete blood count
cDNA ..... complementary deoxyribonucleic acid
CFR ..... Code of Federal Regulations
CLIA ..... Clinical Laboratory Improvement Amendments
CM ..... centimeter
CMV ..... cytomegalovirus
COL7A1 ..... Collagen 7 gene
cPPT ..... central polypurine tract
CRF ..... case report form
CTC ..... Common Toxicity Criteria
DIF ..... direct immunofluorescence
DMEM ..... Dulbecco's Modified Eagle Medium
DNA ..... deoxyribonucleic acid
DSMB ..... data safety monitoring board
EB ..... epidermolysis bullosa
EDTA ..... ethylenediamine tetraacetic acid
ELISA ..... enzyme-linked immunosorbent assay
EM ..... electron microscopy
FAS ..... Full analysis set
FACS ..... Fluorescence-activated cell sorting
FDA ..... Food and Drug Administration
GCP ..... Good Clinical Practice
HA ..... hemaglutinin tag
HDF ..... Human Dermal Fibroblasts
HEENT ..... head, ears, eyes, nose, throat
Hep ..... hepatitis
HIPAA ..... Health Insurance Portability and Accountability Act
HIV ..... human immunodeficiency virus
ICF ..... informed consent form
I/E ..... inclusion / exclusion
IEM ..... immunoelectron microscopy

IF ..... immunofluorescence
Ig..... immunoglobulin
IND ..... Investigational New Drug application
IP ..... Investigational Product
IRB..... Institutional Review Board
KAN^r..... kanamycin resistance
LLN ..... lower limit of normal
LTFU..... long-term follow-up
LTR..... long terminal repeat
mAb ..... monoclonal antibody
MCH..... mean corpuscular hemoglobin
MCHC ..... mean corpuscular hemoglobin concentration
MCV..... mean cell volume
MCS..... multiple cloning site
mRNA ..... messenger ribonucleic acid
NC1 ..... non-collagenous region 1 of the collagen 7 molecule
NC2 ..... non-collagenous region 2 of the collagen 7 molecule
NCI ..... National Cancer Institute
NIH ..... National Institute of Health
OCT ..... optimum cutting temperature compound
PCR ..... polymerase chain reaction
PHI..... protected health information
PI ..... Principal Investigator
PP..... per protocol
qPCR ..... quantitative polymerase chain reaction
qRT-PCR ..... quantitative real time polymerase chain reaction
RBC ..... red blood cell count
RCL ..... replication competent lentivirus
RDEB..... recessive dystrophic epidermolysis bullosa
RDW ..... red blood cell distribution width
RNA ..... ribonucleic acid
SAE ..... serious adverse event
SAP ..... statistical analysis plan
SCC ..... squamous cell carcinoma
SIN-LV ..... self-inactivating lentivirus
VSV-G..... Vesicular Stomatitis Virus-G
WBC ..... white blood cell
WPRE ..... Woodchuck Hepatitis Posttranscriptional Regulatory Element
WT ..... wild type

Protocol Synopsis

Title	A Phase I/II Study of FCX-007 (Genetically-Modified Autologous Human Dermal Fibroblasts) for Recessive Dystrophic Epidermolysis Bullosa (RDEB)
Statement of Purpose	The purpose of this study is threefold: - To evaluate the safety of FCX-007 - To evaluate C7 expression and the presence of anchoring fibrils resulting from FCX-007 - To analyze wound healing as a result of FCX-007 administration
Objectives	**Primary** 1) The primary objective of this protocol is to evaluate the safety of FCX-007. **Secondary** 1) To evaluate mechanism of action of FCX-007 at visits 5 (Week 4), 6 (Week 12), 8 (Week 25), 10 (Week 52), and unscheduled visits through the evaluation of skin biopsies for C7 expression and the presence of anchoring fibrils. 2) To evaluate the efficacy of FCX-007 through an intra-subject paired analysis of target wound area at visits 5 (Week 4), 6 (Week 12), 8 (Week 25),10 (Week 52), and unscheduled visits, comparing FCX-007 treated wounds to untreated wounds through investigator assessment of wound healing based on the digital images of wounds.
Study Drugs	**Test Product:** FCX-007 (Genetically Modified Autologous Human Dermal Fibroblasts)
# of Subjects	Up to 12
Study Design	This is a Phase I/II Study of FCX-007 (Genetically-Modified Autologous Human Dermal Fibroblasts) for Recessive Dystrophic Epidermolysis Bullosa (RDEB) being conducted by Fibrocell to evaluate FCX-007 in subjects with RDEB. Up to twelve subjects will be enrolled, up to six (6) in Phase I, and up to six (6) in Phase II. Phase I will enroll adult subjects only; Phase II can enroll adults and pediatric subjects (aged seven (7) or older). Within Phase I, subjects will be assigned to one of two arms: subjects with NC1+ status will be enrolled into Arm A and subjects with NC1- status will be enrolled into Arm B. The arms will enroll independently. In Phase I, the study may enroll an equivalent number of subjects to Arm A and Arm B (n=3 each arm). One administration of FCX-007 will consist of a maximum of 15 mL of FCX-007 administered in sixty (60) 0.25 mL intradermal injections. The majority of the injections will be administered around the margin of target wounds and at least 6 injections will be administered to intact skin. The Investigator will attempt to administer all of the 15mL of FCX-007. This will be accomplished by selecting target wounds that are as close as possible to 54 linear cm, leaving at least 6 administrations for intact skin, for a total of 60 injections. For the wound administrations, subjects will receive FCX-007 administered intradermally to one, two or three paired target wounds at Visit 3 (Day 0). Subjects receive a second administration to wounded and/or intact skin at Visit 5 (Week 4). In this study, one wound in each target wound pair will be used as a control for efficacy and safety evaluations. FCX-007 administered wounds will be compared

within paired target wounds to untreated wounds.

As there is no previous human experience with FCX-007, treatment administration will be staggered in two places:

1. Between the first and second enrolled subjects in each arm.
2. Between the third and fourth enrolled subjects in each arm.

Proceeding to administration of FCX-007 after a stagger requires that the previous subject complete Week 4 evaluations and the Investigator must have received approval from the Data Safety Monitoring Board (DSMB) to continue the study prior to the next adult subject's FCX-007 administration.

At a minimum, FDA and DSMB approvals are required for enrollment of pediatric subjects. Local oversight committees may also require approval.

Each phase of the study is divided into four (4) periods: Screening, Wound Monitoring, 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 FCX-007 manufacturing, and the identification and photography of potential target wounds. FCX-007 manufacturing requires about 4 months. This period is the Wound Monitoring Period. Subject target wounds may be imaged a minimum of two times (at least 4 weeks apart) during this period. The purpose of the imaging is to identify wounds with the most consistent wound areas that meet criteria, and to establish a baseline area that takes into account natural wound area variation. The Wound Monitoring Period is expected to have a duration of approximately four months; however, this period can extend beyond four months to accommodate patient scheduling, variations in manufacturing duration and protocol mandated delays (i.e. pauses due to staggered treatment).

After FCX-007 manufacturing is complete, Fibrocell (the Sponsor) and the Investigator will mutually agree on the date of receipt of FCX-007. The duration of the Treatment Period may fluctuate between two and four days to accommodate subject safety and scheduling. The Treatment Period visits (Day -2 to Day 2) will be scheduled so that the day of dosing (Day 0) is the day of receipt of FCX-007. Prior to dosing, wounds are identified that meet treatment criteria based on imaging results obtained. Up to three pairs of target wounds may be identified for each subject and the Investigator will pair the target wounds according to similarity in wound area.

One wound in each pair will receive FCX-007 and the other wound no treatment.

Safety and proof of mechanism evaluations are conducted during site visits at Visits 5 (Week 4), 6 (Week 12), 8 (Week 25) and 10 (Week 52), and unscheduled visits. Proof of mechanism will be monitored through assays conducted on biopsies taken from target wounds and areas of intact skin in which FCX-007 was administered.

Safety is monitored throughout the study, captured during on-site visits and while the subject is off-site through adverse event diaries. The following assessments in each subject will be assessed: adverse events (AEs), physical examinations, vital signs, clinical laboratory evaluations (including C7 antibodies, and RCL), medical history, and prior/concomitant medications, as appropriate. A DSMB will periodically review subject safety data.

The Long-Term Follow-Up is a 15-year period following Week 52/ET in which safety is monitored (including RCL testing yearly and any new malignancies to 15-years) at a minimum annually. If all post-treatment RCL assays are negative during the first year (e.g., Weeks 4, 12, 16, 25, 32, and 52), collection of the yearly follow-up samples will be discontinued.

Population

Inclusion Criteria

1. Age
    a. Phase I: Eighteen (18) years old or older.
    b. Phase II: Seven (7) years old and older.
2. Diagnosis of recessive dystrophic epidermolysis bullosa (RDEB) (inclusive) by:
    a. Clinical diagnosis
    b. Immunofluorescence (IF) evaluation
    c. Electron microscopy (EM/IEM) evaluation
    d. Confirmation of RDEB C7 mutations in the subject
3. NC1 Status
    a. Arm A: Positive for the NC1 domain of C7 (NC1+) as determined by results of genetic testing showing one or no loss of function mutations in exons 1-28
    b. Arm B: Negative for the NC1 domain of C7 (NC1-) as determined by results of genetic testing showing two loss of function mutations in exons 1-28)
4. NC2 Status: negative or weakly positive for LH24 antibody staining as determined by immunoelectron microscopy (IEM).
5. Subjects and guardians, who are, in the opinion of the Investigator, able to understand the study, co-operate with the study procedures and are willing to return to the clinic for all the required follow-up visits.

Exclusion Criteria

1. Medical instability limiting ability to travel to the investigative center.
2. Active infection with HIV, hepatitis B or hepatitis C, as determined by hepatitis B surface antigen screening, detection of hepatitis C antibodies, or positive result of hepatitis C PCR analysis.
3. The presence of antibodies to the basement membrane of monkey esophagus by indirect immunofluorescence using the subject's serum.
4. Evidence of systemic infection.
5. Current evidence of metastatic squamous cell carcinoma at the site to be injected.
6. Known allergy to any of the constituents of the product.
7. Active drug or alcohol addiction.
8. Hypersensitivity to anesthesia chosen (lidocaine/prilocaine cream, moderate sedation, general anesthesia).
9. Receipt of a chemical or biological study product for the specific treatment of RDEB in the past six months
10. Women who are pregnant or breast-feeding.
11. Any clinically significant abnormal laboratory result from Day -2 (Grade 2 or higher on the National Cancer Institute [NCI] toxicity scale), except for the following:
    a. Albumin < 2.5 g/dL,
    b. Leukocytes > 20K/uL,
    c. Hemoglobin < 7.5 g/dL
12. Clinically significant abnormalities (Grade 2 or higher on the NCI toxicity scale) identified through medical history and physical examination at Day 0, with the following exceptions:

	a. Anorexia, can enroll up to Grade 4 (inclusive) b. Constipation, can enroll up to Grade 2 (inclusive) c. Dysphagia, can enroll up to Grade 4 (inclusive) d. Keratitis, can enroll up to Grade 4 (inclusive) e. Bone pain, can enroll up to Grade 2 (inclusive)
Test Product, Dose, Mode of Administration	One set of three 3-4 mm biopsies obtained at Screening from non-blistered skin will be used to manufacture up to 20 mL of FCX-007 for use in this protocol. A maximum of fifteen (15) mL of FCX-007 will be administered intradermally on at visit 3 (Day 0) in up to sixty (60) 0.25 mL injections. The maximum total administered dose will consist of up to [redacted] genetically modified fibroblast cells. Up to an additional 15 mL will be administered on Visit 5 (Week 4). FCX-007 will be packaged in 2 mL cryovials, each containing 1.2 mL for withdrawal of 1 mL. After a 21-gauge needle is used to withdraw FCX-007 from the vial, the needle is replaced with a 30-gauge needle prior to injection.
Duration of Treatment	Treatment is administered once at Day 0 (Visit 3) and again at Visit 5 (Week 4).
Safety Evaluations	Safety will be monitored throughout the study. The following assessments in each subject will be assessed: adverse events (AEs), physical examinations, vital signs, clinical laboratory evaluations, medical history, and prior/concomitant medications. Specifically, the following will be assessed for adverse events: - Changes in laboratory values, including: • C7 Antibodies as assayed by linear basement membrane zone (BMZ) staining for IgM, IgG, IgA or serum IgG antibodies binding to the epithelium of monkey esophagus with a basement membrane or superficial dermal pattern by indirect immunofluorescence (IIF) microscopy • Direct immunofluorescence (DIF) of subject's skin biopsy staining for IgM, IgG, IgA or complement staining in a linear BMZ distribution localizing to the dermal-epidermal junction • Replication Competent Lentivirus (RCL) • Complete Blood Count with Differential - Changes in vital signs: blood pressure, heart rate, respiratory rate, temperature - Change in physical exam - Long-term safety follow-up including: • Delayed adverse events for at least 15 years in which safety is monitored at a minimum annually. • Replication Competent Lentivirus evaluation yearly for up to 15 years. If all post-treatment assays are negative during the first year (e.g., Weeks 4, 12, 16, 25, 32, and 52), collection of the yearly follow-up samples will be discontinued. • Any new malignancies to Year 15
Proof of Mechanism Evaluations	The following will be investigated to evaluate proof of mechanism: - Expression of C7 as determined by immunofluorescence (IF). - The presence of mature anchoring fibrils as determined by immunoelectron microscopy (IEM). - The change in the treated target and control wounds area from baseline (Day 0) based on investigator assessment of wound healing.

1 Background

1.1 Disease Background

Recessive dystrophic epidermolysis bullosa (RDEB) is an autosomal recessive, inherited skin disease caused by null mutations within the C7 gene (COL7A1). Mutations in COL7A1 have been shown conclusively to underlie dystrophic epidermolysis bullosa (Dang, 2008). The mutations cause an absence or reduction of functional C7 and anchoring fibrils. Anchoring fibrils may be reduced in number and show abnormal morphology (loss of fan-shaped appearance and central cross-banding) or, in the clinically most severe cases, the anchoring fibrils are barely detectable; where only a few thin structures can be seen (Tidman, 1985).

Subtypes of RDEB share in common a deficiency of C7 (Intong, 2012) and this deficiency is the basis upon which diagnosis is made. The disease is characterized by a mechanical fragility and repeated blister formation, potentially occurring on all epithelial-surfaced or lined structures. Blister formation occurs in the basal laminal layer, specifically in the sub-lamina densa, at the level of the structurally defective anchoring fibrils (Dunnill, 1996). They can be long-term, large and severely painful blisters that result from minor skin trauma. COL7A1 contains 118 exons composed of a noncollagenous domain 1 (NC1) (exons 1-28), a central collagenous domain with Gly-X-Y region (exons 29-111), and a noncollagenous domain 2 (NC2) (exons 112 – 118) that catalyzes the anchoring fibril assembly. RDEB patients may either express the NC1 amino-terminal fragment of type VII collagen NC1[+] or lack it (NC1[-]). Epitope mapping of autoantibodies in patients with acquired autoimmunity to type VII collagen (epidermolysis bullosa acquisita) demonstrates that NC1 is the predominant domain targeted by patient autoantibodies These studies suggest that NC1 is likely the most antigenic portion of the type VII collagen molecule. Subjects whose fibroblasts demonstrate expression of the NC1 domain by Western blot analysis should have a reduced chance of an immune response to the therapeutic gene product, type VII collagen. These subjects' immune systems will have recognized the most antigenic portion of the type VII collagen molecule, the NC1 domain, as self, thus reducing potential immune reactions.

Persistent blistering begins at birth and contributes to the high mortality risk due to bacterial infection. In a study of 41 RDEB patients, the infectious causes of pneumonia and sepsis resulted in death in 14.6% and 9.8% respectively (Fine, 2010). Patients who survive bacterial sepsis during early infancy are at a high risk of later developing more severe complications such as growth retardation due to gastrointestinal involvement (Fine, 2008), multifactorial anemia, esophageal strictures, corneal scarring and/or progressive blindness (Fine, 2004), post streptococcal glomerulonephritis, renal failure, progressive hand and foot deformities such as pseudosyndactyly (Fine, 2005), muscle contractures that restrict movement, anemia, esophageal strictures (Fine, 2008), microstomia, obliteration of the oral vestibule, dysphagia, rapid tooth decay, nail deformities, and hair loss. In addition, patients with the severe generalized subtype have an increased lifetime risk (over 90%) (RAC, 2007) of developing aggressive squamous cell

carcinoma. 87% die by the age of 45 due to metastatic squamous cell carcinoma (Fine, 2010).

Currently there is no effective therapy for this disease. Nearly 10% of RDEB patients die before the age of 10, almost 40% by the age of 20, and 72% before the age of 30. Death is usually the result of aggressive squamous cell carcinoma, sepsis, or of malnutrition due to an inability or unwillingness to eat due to mouth or esophagus involvement (RAC, 2007).

1.2 FCX-007 Background

1.2.1 Cell Manufacturing

FCX-007 is an autologous cell product manufactured by *ex vivo* gene modification and expansion of dermal fibroblasts obtained from one set of three 3-4 mm biopsies of the patient's skin. The biopsies are shipped in a sterile buffer solution to a central manufacturing facility, where they are digested with enzymes to release the fibroblast cells, which are then seeded into a tissue culture vessel. The cells are expanded, transduced with INXN-2004 (a lentiviral vector encoding the functional COL7A1 gene), and expanded further to obtain a sufficient quantity for study treatment. Cells undergo Drug Substance release testing. The Drug Product for patient injection is shipped same day or overnight prior to each scheduled day of investigational treatment. FCX-007 Drug Substance is evaluated against Drug Product release specifications. FCX-007 Drug Product is shipped refrigerated for overnight delivery to the clinic and is to be administered prior to the expiration date and time indicated on the product label. FCX-007 cells are injected intradermally at the periphery of RDEB wounds as well as into intact skin.

1.2.2 INXN-2004 (LV-COL7 Lentivirus) Construction and Characterization

The COL7A1 gene is introduced to the cultured Fibroblast cells using INXN-2004 (a recombinant Lentiviral Vector (LV) encoding the COL7A1 gene). The LV is a replication incompetent, Vesicular Stomatitis Virus-G (VSV-G) pseudotyped, self-inactivating lentivirus (SIN-LV) that expresses human COL7A1 gene under the CMV promoter.

Figure 1 – INXN-2004 Vector Map

1.2.2.1 COL7A1 Gene

The full length human COL7A1 gene (8835 base pairs (bp)) was assembled at Intrexon Corporation from fragments sourced from reverse transcription of human RNA, commercial plasmid (Origene plasmid SC300011), and DNA synthesis. The full length human COL7A1 gene was cloned into an expression vector at Intrexon. The COL7A1 gene was subsequently cloned into an LV vector to produce INXN-2004.

1.2.3 Preclinical

In vitro and *in vivo* studies were conducted to assess FCX-007 safety as well as the ability to confer formation of anchoring fibrils and correction of the RDEB phenotype in human organ cultures and human skin grafted onto immunodeficient mice.

1.2.3.1 In vitro Assessment of FCX-007

In vitro pharmacology analyses were conducted on FCX-007 cells to evaluate copy number of integrated LV-COL7, mRNA and protein expression of C7, and functionality of the C7 expressed by FCX-007. *In vitro* pharmacology analysis of FCX-007 demonstrated that the COL7A1 gene integrated into RDEB cells (transduced) using INXN-2004. Following cell passaging and amplification post-transduction, integration of INXN-2004 in FCX-007 cells averaged 0.41 to 0.74 copies per cell. The resulting transduced RDEB cells (FCX-007) expressed C7 protein. The expression of C7 was demonstrated through:

- Indirect immunofluorescence (IIF) showing C7 staining on FCX-007 cells,

- Flow cytometry demonstrating that up to 30% of the FCX-007 cells are positive for C7 expression, and,
- An enzyme-linked immunosorbent assay (ELISA) demonstrating C7 expression from FCX-007 cells at 1966 to 2313 ng/day/million cells.

Additional assays demonstrated that FCX-007 C7 was predominantly trimeric, specifically bound to Laminin332, and reversed an RDEB hypermotility phenotype.

1.2.3.2 In vivo Toxicology Assessment of FCX-007

The safety and biodistribution of FCX-007 was evaluated in a 6-month toxicology/toxicokinetics study in NSG mice injected subcutaneously with six doses of FCX-007. FCX-007 was well tolerated throughout the 3 and 6-month timepoints. GM-HDF did not result in cell-related mortality, adverse clinical observations or changes in body weights. There were no toxicologically important differences in organ weights or clinical pathology parameters and no GM-HDF-related gross pathology or histopathology findings in the male and female mice throughout the study. No adverse palpable masses related to administration of GM-HDF or tumorigenic potential was observed. PCR evaluation detected presence of low levels of vector DNA and/or RNA expression in skin in the male and female animals at 3 months confirming exposure to GM-HDF. PCR evaluation revealed a general lack of persistence of the cells and expression in the NSG mice to the 6-month timepoint. No test article-related findings were observed.

2 Rationale and Objectives

2.1 Rationale

Fibrocell is developing FCX-007 in anticipation of improving skin function in RDEB patients through restoration of type VII collagen and anchoring fibril levels.

2.2 Objectives

2.2.1 Primary

1) The primary objective of this protocol is to evaluate the safety of FCX-007.

2.2.2 Secondary

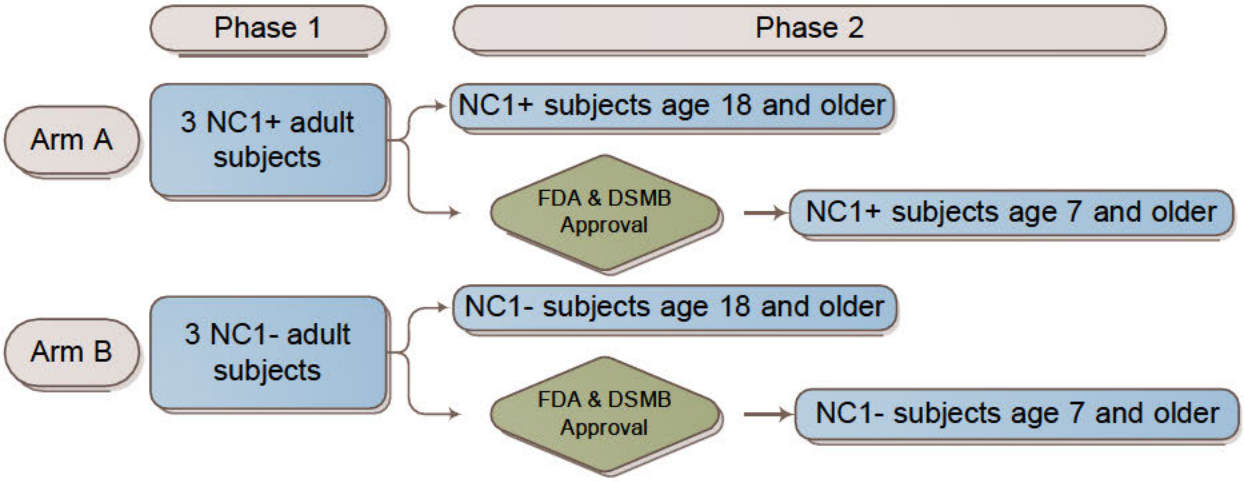
1) To evaluate mechanism of action of FCX-007 at visits 5 (Week 4), 6 (Week 12), 8 (Week 25), 10 (Week 52), and unscheduled visits through the evaluation of skin biopsies for C7 expression and the presence of anchoring fibrils.
2) To evaluate the efficacy of FCX-007 through an intra-subject paired analysis of target wound area at visits 5 (Week 4), 6 (Week 12), 8 (Week 25), 10 (Week 52), and unscheduled visits, comparing FCX-007 treated wounds to untreated wounds through investigator assessment of wound healing based on the digital images of wounds.

3 Experimental Plan

3.1 Study Design

This is a Phase I/II Study of FCX-007 (Genetically-Modified Autologous Human Dermal Fibroblasts) for Recessive Dystrophic Epidermolysis Bullosa (RDEB) being conducted by Fibrocell to evaluate FCX-007 in subjects with RDEB. Up to twelve subjects will be enrolled, up to six (6) in Phase I, and up to six (6) in Phase II. Phase I will enroll adult subjects only; Phase II can enroll adults and pediatric subjects (aged seven (7) or older). Within Phase I, subjects will be assigned to one of two arms: subjects with NC1+ status will be enrolled into Arm A and subjects with NC1- status will be enrolled into Arm B. The arms will enroll independently.
In Phase I, the study may enroll an equivalent number of subjects to Arm A and Arm B (n=3 each arm). In Phase II, the study will target enrolling 3 subjects to each arm, but will allow a disproportionate distribution of subjects between Arm A and Arm B to equal 6 total subjects.

Figure 2 - High-Level Study Design



One administration of FCX-007 will consist of up to sixty (60) 0.25 mL intradermal injections in wounded and/or intact skin. The majority of the injections will be administered around the margin of target wounds and at least 6 injections will be administered to intact skin. The Investigator will attempt to administer all 15mL of FCX-007. This will be accomplished by selecting target wounds that are as close as possible to 54 linear cm, leaving at least 6 administrations for intact skin, for a total of 60 injections.

For the wound administrations, subjects will receive FCX-007 administered intradermally to one, two or three paired target wounds at Visit 3 (Day 0). Subjects will receive a second administration to wounded and/or intact skin at Visit 5 (Week 4).

In this study, one wound in each target wound pair will be used as a control for efficacy and safety evaluations. FCX-007 administered wounds will be compared within paired target wounds to untreated wounds.

As there is no previous human experience with FCX-007, treatment administration will be staggered in two places:

1. Between the first and second enrolled subjects in each arm.
2. Between the third and fourth enrolled subjects in each arm.

Proceeding to administration of FCX-007 after a stagger requires that the previous subject complete Week 4 evaluations and the Investigator must have received approval from the Data Safety Monitoring Board (DSMB) to continue the study prior to the next subject's FCX-007 administration.

At a minimum, FDA and DSMB approvals are required for enrollment of pediatric subjects. Local oversight committees may also require approval.

Each phase of the study is divided into four (4) periods: Screening, Wound Monitoring, 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 FCX-007 manufacturing, and the identification and photography of potential target wounds. FCX-007 manufacturing requires about 4 months. This period is the Wound Monitoring Period. Subject target wounds may be imaged a minimum of two times (at least 4 weeks apart) during this period. The purpose of the imaging is to identify wounds with the most consistent wound areas that meet criteria, and to establish a baseline area that takes into account natural wound area variation. The Wound Monitoring Period is expected to have a duration of approximately four months; however, this period can extend beyond four months to accommodate patient scheduling, variations in manufacturing duration and protocol mandated delays (i.e. pauses due to staggered treatment).

After FCX-007 manufacturing is complete, Fibrocell (the Sponsor) and the Investigator will mutually agree on the date of receipt of FCX-007. The duration of the Treatment Period may fluctuate between two and four days. The Treatment Period visits (Day -2 to Day 2) will be scheduled so that the day of dosing (Day 0) is the day of receipt of FCX-007. Prior to dosing, wounds are identified that meet treatment criteria based on imaging results obtained. Up to three pairs of target wounds may be identified for each subject and the Investigator will pair the target wounds according to similarity in wound area.

One wound in each pair will receive FCX-007 and the other wound no treatment.

Safety and proof of mechanism evaluations are conducted during site visits at Visits 5, 6, 8 and 10 (weeks 4, 12, 25, 52), and unscheduled visits. Proof of mechanism will be monitored through assays conducted on biopsies taken from target wounds and areas of intact skin in which FCX-007 was administered.

Safety is monitored throughout the study, captured during on-site visits and while the subject is off-site through adverse event diaries. The following assessments in each subject will be assessed: adverse events (AEs), physical examinations, vital signs, clinical laboratory evaluations (including C7 antibodies, and RCL), medical history, and prior/concomitant medications, as appropriate. A DSMB will periodically review subject safety data.

The Long-Term Follow-Up is a 15-year period following Week 52/ET in which safety is monitored (including RCL testing yearly and any new malignancies to 15-years) at a minimum annually. If all post-treatment RCL assays are negative during the first year (e.g., Weeks 4, 12, 16, 25, 32, and 52), collection of the yearly follow-up samples will be discontinued.

3.2 Number of Investigative Sites

One (1) to three (3) investigative sites will participate in the study.

3.3 Number and Source of Subjects

The enrollment target is up to twelve (12) subjects: Up to six subjects in Phase I and up to six (6) subjects in Phase II. A seventh subject may be enrolled into Phase II at the discretion of the sponsor.

In Phase I, 3 NC1+ subjects may be enrolled to Arm A and 3 NC1- subjects may be enrolled to Arm B. In Phase II, the study will target enrolling 3 subjects to each arm, but will allow a disproportionate distribution of subjects between Arm A and Arm B to equal 6 total subjects. All potential subjects must be properly consented, meet all inclusion/exclusion criteria, and undergo all screening procedures to be eligible for participation in this study.

3.4 Estimated Study Duration

The duration is about 20 months per subject, including the Screening, Wound Monitoring and Treatment Periods. Recruitment is anticipated to take approximately 8 months, resulting in total study duration of approximately 28 months. The end of Treatment Period Visit is scheduled to occur at the end of the 12-month treatment phase. Safety data will continue to be collected by clinic visit or telephone contact approximately every 1 year for at least 15 years after the treatment phase.

4 Subject Eligibility

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (e.g. gender, age, race) and outcome of the screening process (e.g. enrolled into study, reason for ineligibility, or refused to participate).

4.1 Inclusion Criteria

To be eligible for inclusion, each subject must fulfill each of the following criteria:

1. Age
   a. Phase I: Eighteen (18) years old or older.
   b. Phase II: Seven (7) and older.
2. Diagnosis of recessive dystrophic epidermolysis bullosa (RDEB) (inclusive) by:
   a. Clinical diagnosis
   b. Immunofluorescence (IF) evaluation
   c. Electron microscopy (EM/IEM) evaluation
   d. Confirmation of RDEB C7 mutations in the subject
3. NC1 Status
   a. Arm A: Positive for the NC1 domain of C7 (NC1+) as determined by genetic testing results showing one or no loss of function mutations in exons 1-28.
   b. Arm B: Negative for the NC1 domain of C7 (NC1-) as determined by genetic testing results showing two loss of function mutations in exons 1-28.
4. NC2 Status: negative or weakly positive for LH24 antibody staining as determined by immunoelectron microscopy (IEM).
5. Subjects and guardians, who are, in the opinion of the Investigator, able to understand the study, co-operate with the study procedures and are willing to return to the clinic for all the required follow-up visits.

4.2 Exclusion Criteria

Subjects will be excluded from the study if any of the following criteria are met:

1. Medical instability limiting ability to travel to the investigative center.
2. Active infection with HIV, hepatitis B or hepatitis C, as determined by hepatitis B surface antigen screening, detection of hepatitis C antibodies, or positive result of hepatitis C PCR analysis.
3. The presence of antibodies to the basement membrane of monkey esophagus by indirect immunofluorescence using the subject's serum.
4. Evidence of systemic infection.
5. Current evidence of metastatic squamous cell carcinoma at the site to be injected.
6. Known allergy to any of the constituents of the product.
7. Active drug or alcohol addiction.
8. Hypersensitivity to anesthesia chosen (lidocaine/prilocaine cream, moderate sedation, or general anesthesia).
9. Receipt of a chemical or biological study product for the specific treatment of RDEB in the past six months
10. Women who are pregnant or breast-feeding.
11. Any clinically significant abnormal laboratory result from Day -2 (Grade 2 or higher on the National Cancer Institute [NCI] toxicity scale), except for the following:
    a. Albumin < 2.5 g/dL,
    b. Leukocytes > 20K/uL,
    c. Hemoglobin < 7.5 g/dL
12. Clinically significant abnormalities (Grade 2 or higher on the NCI toxicity scale) identified through medical history and physical examination at Day 0, with the following exceptions:
    a. Anorexia, can enroll up to Grade 4 (inclusive)
    b. Constipation, can enroll up to Grade 2 (inclusive)
    c. Dysphagia, can enroll up to Grade 4 (inclusive)
    d. Keratitis, can enroll up to Grade 4 (inclusive)
    e. Bone pain, can enroll up to Grade 2 (inclusive)

5 Subject Enrollment and Withdrawal

Written protocol and informed consent approval are required from the IRB prior to enrollment. Assent form approval is required from the IRB prior to enrolling subjects below the age of consent. All subjects or their respective legal guardians must personally sign and date the relevant consent and/or assent form before enrollment.

5.1 Subject Identification and Number Assignment

Subjects who sign the informed consent form will be assigned a 4-digit subject identification number. Subject identification numbers will begin with “XX” = pre-defined site number, and end with “XX” = subject number (sequential, starting with 01). This number will identify the subject throughout the study and must be used on all study documentation related to that subject.

5.2 Concomitant Therapy and Skin Care

There are no restrictions on concomitant therapies and skin care. Throughout the study, any concomitant medications or treatments deemed necessary to provide adequate supportive care may be prescribed. In particular, medication should be considered during and after the injections to treat pain and/or anxiety (i.e. lorazepam). Routine skin care for RDEB patients will continue throughout the study.

5.3 Withdrawal of Subjects

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:

1. Consent/assent is withdrawn
2. The subject refuses treatment and/or procedures/observations.
3. Occurrence of unmanageable adverse events, or pregnancy.
4. For other reasons (e.g., significant protocol violation, non-compliance).
5. The Sponsor may be contacted if clarification is required.

The primary reason for withdrawal must be recorded on the CRF. Comments or complaints 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-007 will be asked to continue in the Long-Term Follow-Up Period (Section **7.5**). Subjects who withdraw prior to FCX-007 administration will be considered a screen failure and will be replaced. The Sponsor reserves the right to terminate the study.

6 Investigational Product

Investigational product (IP) utilized in this protocol is FCX-007 (genetically modified autologous human dermal fibroblasts suspended in DMEM).

One administration of FCX-007 is up to 15 mL of cell suspension administered as sixty (60) 0.25 mL intradermal injections. **Table 1** provides details regarding the number of cells, vials and injections per administration.

Table 1 – FCX-007 Cell Count and Injections per Administration

FCX-007 Cells	[redacted]
Concentration of FCX-007 Suspension	[redacted]
# Vials	[redacted]
Injections per Vial	[redacted]
Cells per Injection	[redacted]
Number of Injections	[redacted]

6.1 Manufacturing

6.1.1 FCX-007 Manufacturing

FCX-007 will be manufactured from one set of three 3-4 mm biopsies obtained at the Screening Visit. The biopsies will be placed into sterile phosphate buffered saline (PBS), and shipped at 2-8°C immediately to the manufacturing facility. Upon receipt of the biopsies, FCX-007 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-2004 (a lentiviral vector encoding the functional COL7A1 gene), and expanded further. If the manufacturing process does not yield an FCX-007 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.

For each subject, approximately [redacted] FCX-007 cells will be manufactured for use in this study. Up to [redacted] will be administered at each dose administration. Cells undergo release testing and sent to the Investigative Site for administration on Day 0. The duration between biopsy collection and completion of manufacturing is approximately 120 days (4 months) but can vary due to capacity, technical manufacturing reasons, or clinical protocol required pauses between subjects.

6.2 Labeling, Packaging, Storage and Handling

6.2.1 Packaging and Labeling

6.2.1.1 Packaging

Investigational product will be provided to the Investigative Site as an opaque cell suspension in 2.0 mL cryovials containing approximately 1.2 mL of FCX-007 per vial with a recoverable volume of 1.0 mL per vial.

Up to thirty (30) vials of FCX-007 will be provided per subject; 15 vials for Day 0, and 15 vials for week 4.

6.2.1.2 Labeling

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-007
- Lot Number
- Fill Date and Time
- Expiration Date and Time
- Nominal Conc./Vol.: xe7 cells/mL in 1.0 mL
- Manufactured by Fibrocell Technologies Inc.
- 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.

6.2.2 Storage and Handling

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-007 received. The Sponsor or designee will be permitted upon request to audit the administration procedures and records.

FCX-007 Drug Product will be shipped same day or overnight delivery to the clinic and must be administered prior to the expiration date and time indicated on the product label.

7 Study Visits

This section outlines activities by visit. Additional information about specific procedures and evaluations can be found in Section **8** (**Procedures: FCX-007 Administration to Intact Skin**), Section **9** (**Procedures: FCX-007 Administration to Wound(s)**), and Section **10** (**Procedures: Collection and Evaluation of Biopsies**). Study tests and procedures will be performed only after a signed informed consent is obtained.

During the study, every effort should be made to adhere to the visit schedule and visit windows provided in the Schedule of Events (**Table 2**).

Subject Companions

Subjects will be permitted to bring a companion to study visits. Cost associated with travel to the Investigative Site, including those of a companion, will be paid for by the sponsor with prior approval from the sponsor.

Time Frame Between Subjects

The second subject in each arm will not be treated until after the first subject has completed the 4-week evaluation. The DSMB will meet after the first subject has completed visit 5 (Week 4) to review data and determine whether the second subject in each arm can be treated. Likewise, the fourth subject (and first potential pediatric subject) in each arm will not be treated until after the third subject has completed the 4-week evaluation and the DSMB has reviewed the data. DSMB and FDA approval will be required prior to enrollment of any pediatric subject.

Table 2 - Schedule of Events

	Event	Pre-screen	Visit 1 Screen[1]	Wound Monitoring Period[2]	Treatment Period V2 Day -2[4]	V3 Day 0	V4 Day 2	V5 Wk 4 ± 2d	V6 Wk 12 ± 1wk	*V7 Wk 16*[3]	V8 Wk 25 ± 2wk	*V9 Wk 32*[3]	V10 Wk 52 ± 2wk	LTFU
	Information Letter and Phone Screen	X												
	ICF/ Assent/ HIPAA		X											
	Inclusion / Exclusion Criteria	X	X		X	X								
	Demographics	X	X											
	Medical / Medication History	X	X		X	X			X					
	Concomitant Medications					X	X	X	X	X	X	X	X	
	Adverse Events					X	X	X	X	X	X	X	X	X
	Physical Exam		X			X							X	
	Skin Exam[5]		X	X	X	X	X	X	X	X	X	X	X	
	Vital Signs		X		X	X	X	X	X	X	X	X	X	
	Digital Imaging of Wounds		X	X	X	X	X	X	X	X	X	X	X	
	Target Wound Selection				X									
	Investigator Assessment of Wound Healing							X	X	X	X	X	X	
	Bacterial Culture[6]				X	X	X	X	X	X	X	X	X	
	FCX-007 Administration					**X**		**X**						
Blood and Urine Tests	Urine Pregnancy Test		X		X									
	Hematology & Chemistry		X		X			X	X	X	X	X	X	
	HIV, Hep B, Hep C Testing		X											
	RCL evaluation			X[7]				X	X	X	X	X	X	X[12]
	C7 Antibody Assay		X					X	X	X	X	X	X	
	Genetic Testing		**X**											

Continues on next page

[1] Visit 1 protocol events may take up to 4 days. Screening assays for RDEB diagnosis will not be repeated unless warranted by the Investigator if the subject medical records contain these results.

[2] At least two visits to the site for imaging during the approximate 4 month period in which FCX-007 is being manufactured may occur. The last wound monitoring visit should occur no more than 60 days prior to the injection of FCX-007.

[3] Visits 7 and 9 can be performed in the office or via telephone consult. If visit is conducted via telephone consult, only concomitant medication and adverse event reporting from subject will be recorded.

[4] Subjects can remain at or near the Investigative Site between Visits 2 and 4.

[5] Skin exam on potential target wounds only during wound monitoring visits.

[6] To be performed at Visit 2 and as needed throughout the study if clinical evaluation is indicative of infection.

[7] A blood sample must be collected for RCL baseline assessment either at screening or wound monitoring visits, results must be available prior to Visit 3 (Day 0).

Table 2 - Schedule of Events, Continued

Event			Pre-screen	Visit 1 Screen	Wound Monitoring Period	V2 Day -2	V3 Day 0	V4 Day 2	V5 Wk 4 ± 2d	V6 Wk 12 ± 1wk	V7 *Wk 16*	V8 Wk 25 ± 2wk	V9 *Wk 32*	V10 Wk 52 ± 2wk	LTFU
Biopsies[8]		Three 3-4 mm for FCX-007 manufacture[9]		X											
	Intact Skin	1 for IEM		X[10]			X			X		X		X	
		1 for IF and DIF		X[11]			X		X	X		X		X	
		1 for genomic retention of C7 and mRNA expression[11]					X		X	X		X		X	
	Wounds	1 for IEM								X		X		X	
		1 for IF and DIF								X		X		X	
		1 for genomic retention of C7 and mRNA expression							X	X		X		X	

[8] The number of biopsies collected at a visit may vary based on results from previous visits.
[9] An additional set of biopsies may be collected if the manufacturing process does not yield an FCX-007 cell count sufficient for one administration or do not meet release specifications.
[10] Evaluations do not need to be performed if the subject meets inclusion criteria for RDEB diagnosis.
[11] Samples cannot be shipped on Fridays.
[12] RCL evaluation yearly for up to 15 years. If all post-treatment assays are negative during the first year (e.g., Weeks 4, 12, 16, 25, 32, and 52), collection of the yearly follow-up samples will be discontinued.

7.1 Screening Period

7.1.1 Prescreening

An Investigator or designee will prescreen medical histories of RDEB patients for potential inclusion into this study. Medical information reviewed may include the following and is dependent upon the Investigative Site's receipt of prior authorizations to access the data:

- NC1 status
- NC2 status as determined through LH24 antibody staining
- COL7A1 genotype of the subject
- C7 antibody history
- RDEB diagnosis results as determined by IF and EM/IEM
- Medical history
- Negative direct immunofluorescence (DIF)

The Investigator may request additional PHI disclosure authorizations from the potential subject to assist with Pre-Screening.

Potentially eligible subjects over the age of 18 are mailed an IRB-approved information letter which includes a study overview, key inclusion/exclusion criteria, information about the recruitment process, and contact information. For the Phase II portion of the study, parents of potentially eligible minors will be mailed the IRB-approved information letter.

If a potential subject or parent or guardian contacts the Investigative Site indicating interest in the study, they will be contacted by phone. An Investigator or designee reviews the letter with the subject or parent or guardian, 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 is sent to the potential subject to review.

7.1.2 Informed Consent

The Investigator will be responsible for obtaining from every subject prior to his/her participation in the study an ICF signed by the subject or legally authorized representative, in accordance with the Code of Federal Regulations, Title 21, Part 50.20. For subjects between the ages of 7 and 17 (inclusive), the Investigator is responsible for obtaining assent from the subject and consent from both parents or legal guardians. The ICF/Assent that is used must be the current version and must be approved by both the reviewing IRB and by the Sponsor. Informed consent/assent will be obtained from the subject after a full explanation of the purpose of the study, risks and discomforts involved, potential benefits, etc. have been provided by the Investigator both verbally and in writing. The original signed copy of the informed consent/assent must be maintained in the institution's records and is subject to inspection by a Sponsor representative.

7.1.3 Screening (Visit 1)

Screening evaluations may be conducted over the course of up to 3 days.

To minimize travel requirements in this patient population, manufacturing biopsies can be collected before the subject leaves the clinic on the last day of the screening visit if the subject meets all of the entry criteria for which results are available and has a clinical RDEB diagnosis. It is possible that the following results will not be available at the time that the manufacturing biopsies are taken:

- Diagnosis of RDEB by Immunofluorescence (IF)
- Diagnosis of RDEB by Electron microscopy (EM/IEM)
- Diagnosis of RDEB by Confirmation of RDEB C7 mutations in the subject
- Infectious disease panel (HIV, hepatitis B, hepatitis C) results
- NC1 status
- NC2 status

If manufacturing biopsies are not taken at the Screening visit, they may be taken at Wound Monitoring Visit 1.

The following evaluations are conducted as part of the screening visit:

- Review and signing of informed consent/assent.
- Collection of demographic data (e.g. sex, age, race, and ethnicity)
- Inclusion/exclusion criteria
- Medical history including respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric and other diseases.
- Medication history
- Physical and Skin Exam
- Vital signs: blood pressure, heart rate, respiratory rate, temperature
- Collection of blood (approximately 22.5 mL) for clinical laboratory tests:
    - Serum chemistry
    - Hematology
    - HIV, Hep B, Hep C
    - RCL (this baseline blood sample may be collected at a wound monitoring visit. Results must be available prior to Day 0)
    - C7 antibody assay
- Collection of urine for pregnancy test, if applicable
- Digital imaging of wounds

- Identification of potential target wounds and labeling the selected wounds with sequential number of P01 through Pnn.
- Collection of one set of three (3) 3-4 mm biopsies for the manufacturing of FCX-007
- The following evaluations are required only if RDEB diagnosis documentation is not available to support entry into this protocol:
    - Collection of biopsy for EM/IEM
    - Collection of biopsy for IF and DIF
    - Collection of blood for genetic testing and determination of NC1 status
- Once all screening data is available, the PI will complete screening assessment. The subject will not be scheduled for or receive treatment until the Investigator confirms all inclusion/exclusion criteria have been met. If screening tests results received after manufacturing biopsies have been taken show the subject does not meet study criteria, the subject will be withdrawn and all material obtained for manufacturing will be destroyed unless consent has been obtained to use the tissue for future research.

7.2 Wound Monitoring Period

The Wound Monitoring Period may consist of 2 or more visits during the 4-month period in which FCX-007 is being manufactured. The purpose of the visits is to image potential target wounds. Potential target wounds will also undergo a skin examination during these visits. The overall length of the Wound Monitoring Period may vary due to manufacturing or data analysis. The first visit may be scheduled at least 30 days after the Screening visit and subsequent visits may be scheduled at least 30 days apart. If possible, the last wound monitoring visit may occur no more than 60 days prior to the injection of FCX-007.

Because the length of the manufacturing period may vary, the wound monitoring visits should be based on the best available estimates of when the first injection will be available.

If insufficient cell growth occurs and FCX-007 cannot be manufactured, subjects will be asked for additional manufacturing biopsies.

Collection of blood for RCL analysis can be obtained at a wound monitoring visit if not taken at screening. Results must be available prior to Day 0.

Manufacturing biopsies can be taken at Wound Monitoring Visit 1 if not obtained at the Screening Visit.

7.3 Visits 2 through 10

Study procedures are scheduled at Visits 2 (Day -2), 3 (Day 0), 4 (Day 2), 5 (Week 4), 6 (Week 12), 7 (Week 16), 8 (Week 25), 9 (Week 32), and 10 (Week 52). The Investigator may extend the subject's stay for any visit at his/her discretion based on any adverse events experienced.

Unscheduled procedures may occur during this period and resulting data should be captured on Unscheduled Visit case report forms. If deemed necessary, Investigators may attend to the subject at the hotel to check on their progress. Nursing support for bandage changes will be provided as needed.

7.3.1 Visit 2 (Wound Selection/Run-In)

Visit 2 procedures may occur up to 2 days (±1 day) prior to the day of FCX-007 administration. The following procedures will be performed during Visit 2:

- Re-evaluation of inclusion/exclusion criteria
- Review of medical and medication history
- Skin Exam
- Vital signs: blood pressure, heart rate, respiratory rate, temperature
- Collection of blood (approximately 12.5 mL) for laboratory tests
    - Serum chemistry
    - Hematology
- Collection of urine for pregnancy test, if applicable
- Bacterial culturing of target wounds
- Final target wound selections of up to 3 pairs from the selected potential target wounds (See Section **9.1** for details)
- Label the selected target wound pairs as T1A and T1B for the 1st pair, T2A and T2B for the 2nd pair, and T3A and T3B for the 3rd pair.
- Digital imaging of wounds.

7.3.2 Visit 3 (Day 0; Day of Injection)

Visit 3 procedures are scheduled to occur on the day of receipt of FCX-007. The following procedures will be performed during this visit:

- Re-evaluation of inclusion/exclusion criteria
- Review of medical and medication history
- Physical and Skin Exam
- Vital signs: blood pressure, heart rate, respiratory rate, temperature
- Bacterial culturing of target wounds (may be done if clinical evaluation is

indicative of infection)

- Surgical marking around the target wounds and on the intact skin
- Digital imaging of injection sites
- Tattoos will be placed on non-blistered skin near the target wounds for the purpose of calibrating the post-dose imaging.
- Tattoos will also be placed next to the intact skin injection sites for the purpose of precisely locating the biopsy sites at follow-up visits.
- Randomly assign each wound of a target wound pair to either active treatment or control (Visit 3 only).
- Biopsy collection to be used as IF/DIF and IEM.
    - Biopsy location markings must be imaged prior to collection.
    - Biopsy collection must occur prior to administration
- FCX-007 administration to target wounds
- FCX-007 administration to the intact skin.
- Post-dose digital imaging
- Post-dose assessment of concomitant medications and adverse events

As noted above, the subject may remain at the Investigative Site or in a nearby hotel for up to 2 days following FCX-007 administration. During this period, the subject will be monitored for autoimmune reactions to FCX-007. At a minimum, subjects will be contacted once per day on days in which there are no scheduled procedures.

7.3.3 Visit 4 (Day 2)

Visit 4 procedures are scheduled to occur up to 2 days (±1 day) after Visit 3. The following procedures will be performed during this visit:

- Assessment of adverse events
- Assessment of concomitant medications
- Skin Exam
- Vital signs: blood pressure, heart rate, respiratory rate, temperature
- Digital imaging of wounds

Following Visit 4, the subject may return home.

7.3.4 Visit 5 (Week 4)

The visit window for the Week 4 visit is ±2 days. The following procedures will be performed during this visit:

- Assessment of adverse events
- Assessment of concomitant medications
- Skin exam
- Vital signs: blood pressure, heart rate, respiratory rate, temperature
- Collection of blood (approximately 19 mL) for laboratory tests:
  - Serum chemistry
  - Hematology
  - Analysis for C7 antibodies
  - RCL analysis
- Digital imaging of wounds
- Investigator Assessment of Wound Healing.
- Bacterial culturing of target wounds (may be done if clinical evaluation is indicative of infection).
- Skin biopsies will be collected for IEM, genomic DNA/mRNA and/or IF/DIF evaluation at the site of Investigational Product/placebo administration as outlined in **Table 2**. Biopsy location markings must be imaged prior to collection.
- Skin biopsies will be collected from intact skin administration sites for IEM, genomic DNA/mRNA and/or IF/DIF evaluation as outlined in **Table 2**.
- Surgical marking around the target wounds and on the intact skin
- Tattoos will be placed on non-blistered skin near the target wounds for the purpose of calibrating the post-dose imaging.
- Tattoos will also be placed next to the intact skin injection sites for the purpose of precisely locating the biopsy sites at follow-up visits.
- FCX-007 administration to target wounds
- FCX-007 administration to the intact skin.
- Post-dose digital imaging
- Post-dose assessment of concomitant medications and adverse events

7.3.5 Visit 6 (Week 12)

The visit window for Week 12 is ±1 week. The following procedures will be performed during these visits:

- Re-evaluation of inclusion/exclusion criteria
- Review of medical history
- Assessment of adverse events
- Assessment of concomitant medications
- Physical and Skin exam
- Vital signs: blood pressure, heart rate, respiratory rate, temperature
- Collection of blood (approximately 19 mL) for laboratory tests:
    - Serum chemistry
    - Hematology
    - Analysis for C7 antibodies
    - RCL analysis
- Digital imaging of wounds
- Investigator Assessment of Wound Healing.
- Bacterial culturing of target wounds (may be done if clinical evaluation is indicative of infection).
- Skin biopsies will be collected for IEM, genomic DNA/mRNA and/or IF/DIF evaluation at the site of Investigational Product/placebo administration as outlined in **Table 2**. Biopsy location markings must be imaged prior to collection.
- Skin biopsies will be collected from intact skin administration sites for IEM, genomic DNA/mRNA and/or IF/DIF evaluation as outlined in **Table 2**.

7.3.6 Visit 7 (Week 16)

Based on the subject's availability to travel, *this visit may be performed via a telephone consult or in the office.* ***If the visit is performed via telephone consult, the investigator and subject/guardian will review adverse events and concomitant medications.*** If the visit is performed in the office, the following procedures will be performed:

- Assessment of adverse events
- Assessment of concomitant medications
- Skin exam
- Vital signs: blood pressure, heart rate, respiratory rate, temperature
- Collection of blood (approximately 19 mL) for laboratory tests:
    - Serum chemistry
    - Hematology

    - Analysis for C7 antibodies
    - RCL analysis
- Digital imaging of wounds
- Investigator Assessment of Wound Healing.
- Bacterial culturing of target wounds (may be done if clinical evaluation is indicative of infection).

7.3.7 Visit 8 (Week 25)

The visit window for Week 25 is ±2 weeks.

The following procedures will be performed:

- Assessment of adverse events
- Assessment of concomitant medications
- Skin exam
- Vital signs: blood pressure, heart rate, respiratory rate, temperature
- Collection of blood (approximately 19 mL) for laboratory tests:
    - Serum chemistry
    - Hematology
    - Analysis for C7 antibodies
    - RCL analysis
- Digital imaging of wounds
- Investigator Assessment of Wound Healing.
- Bacterial culturing of target wounds (may be done if clinical evaluation is indicative of infection)
- Skin biopsies will be collected for IEM, genomic DNA/mRNA and/or IF/DIF as outlined in **Table 2**. Biopsy location markings must be imaged prior to collection.
- Skin biopsies will be collected from intact skin administration sites for IEM, genomic DNA/mRNA and/or IF/DIF evaluation as outlined in **Table 2**.

7.3.8 Visit 9 (Week 32)

Based on the subject's availability to travel*, this visit may be performed via a telephone consult or in the office.* ***If the visit is performed via telephone consult, the investigator and subject/guardian will review adverse events and concomitant medications.*** If the visit is performed in the office, the following procedures will be performed:

- Assessment of adverse events
- Assessment of concomitant medications
- Skin exam
- Vital signs: blood pressure, heart rate, respiratory rate, temperature

- Collection of blood (approximately 19 mL) for laboratory tests:
  - Serum chemistry
  - Hematology
  - Analysis for C7 antibodies
  - RCL analysis
- Digital imaging of wounds
- Investigator Assessment of Wound Healing.
- Bacterial culturing of target wounds (may be done if clinical evaluation is indicative of infection).

7.3.9 Visit 10 (Week 52) / Early Termination (ET)

Week 52 is the final visit of the Treatment Period. The visit window for Week 52 is ±2 weeks. The procedures below are the same to be performed for subjects who terminate early from the study. If a subject refuses or is unable to return for an Early Termination Visit, a local physician may be requested to evaluate the subject. At least 3 documented attempts should be made to contact subjects prior to making a determination of lost to follow-up.

- Assessment of adverse events
- Assessment of concomitant medications
- Physical and skin exam
- Vital signs: blood pressure, heart rate, respiratory rate, temperature
- Collection of blood (approximately 19 mL) for laboratory tests:
  - Serum chemistry
  - Hematology
  - Analysis for C7 antibodies
  - RCL analysis
- Digital imaging
- Investigator Assessment of Wound Healing.
- Bacterial culturing of target wounds (may be done if clinical evaluation is indicative of infection).
- Skin biopsies will be collected for IEM, genomic DNA/mRNA and/or IF/DIF evaluation at the site of Investigational Product/placebo administration as outlined in **Table 2**.
- Skin biopsies will be collected from intact skin administration sites for IEM, genomic DNA/mRNA and/or IF/DIF evaluation as outlined in **Table 2**.

7.4 Unscheduled Visits

Unscheduled procedures will be conducted at the discretion of the Investigator. Procedures may include, but are not limited to physical exam, photographs, skin assessment, investigator assessment of wound healing, skin biopsies, wound cultures, and/or blood draws for lab procedures.

7.5 Long-Term Follow-Up Period

Upon completion of the End of Study / Early Termination Visit, subjects will enter into the Long-Term Follow-Up Period.

7.5.1 Years 1 - 5

At a minimum, subjects will be contacted yearly for at least 5 years. Subjects will be contacted by phone. In addition, the subject's primary care provider will be asked to contact the Investigator regarding any unexpected or serious adverse events. Telephone contact reports will document the discussions and the information obtained will be captured on case report forms. The following activities will occur at the one-year follow-up intervals:

- Collection and analysis of blood sample for RCL testing (can be done remotely).
  - If all post-treatment assays are negative during the first year (e.g., Weeks 4, 12, 16, 25, 32, and 52), collection of the yearly follow-up samples will be discontinued.
- Recording of exposures to mutagenic agents and other medicinal products
- Recording of any new serious adverse events, hospitalizations, or illnesses (including new malignancies, 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).
- Discussion with primary care provider regarding medication and medical history.
- If a skin cancer occurs in the region of the FCX-007 administration, attempts will be made to collect samples of the skin cancer to evaluate cells for the presence of viral vector.

7.5.2 Years 6 – 15

Subjects will continue to be followed-up on an annual basis for at least 15 years following FCX-007 administration. Follow-ups from years 6 to 15 include:

- Collection and analysis of blood sample for RCL testing (can be done remotely).
  - If all post-treatment assays are negative during the first year (e.g., Weeks 4, 12, 16, 25, 32, and 52), collection of the yearly follow-up samples will be discontinued.

- Recording of exposures to mutagenic agents and other medicinal products
- Recording of any new adverse events, hospitalizations, or illnesses (including new malignancies, 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).
- Discussion with primary care provider regarding medication and medical history.

8 Procedures: FCX-007 Administration to Intact Skin

8.1 Skin Selection

Select an area of intact, non-blistered skin. The skin should have the following characteristics:

- It should be an area free of blisters, wounds or contracture tissue as assessed by the Principal Investigator during the Wound Monitoring Period.
- There should be no sign of recent blistering at the time of injection.
- The neck, face, head, groin, hands, feet, joints, and axilla are excluded areas.
- Per the Investigator's judgement, select an area of the body with a minimal likelihood of blistering throughout the trial.

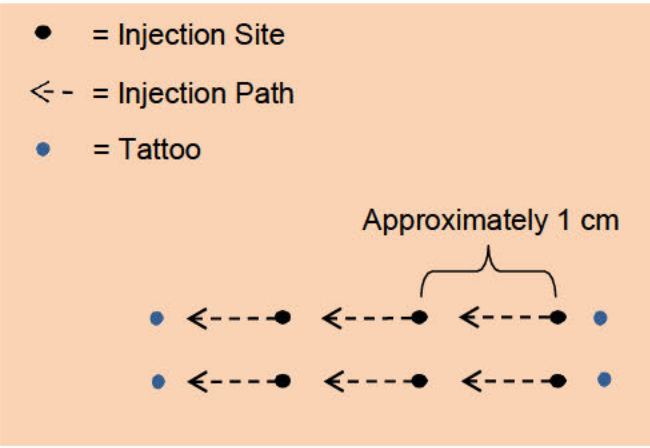
8.2 Determination of the Number of Administrations

FCX-007 will be administered to at least 6 and up to 12 intact skin injection sites. It will only be possible to administer FCX-007 to more than 6 sites if less than 54 injections are administered to the target wound(s).

8.3 Skin Markings

At Visit 3 (Day 0) and Visit 5 (Week 4), use a surgical marker to place dots on the skin 1 cm apart in a linear array. Place tattoos so that the ends of the administration rows can be identified (**Figure 3**) at future visits.

Figure 3 - Intact Skin Grid



8.4 Imaging

The intact skin grid will be imaged at baseline after the skin markings have been applied. This image will be used as a reference for biopsies at follow-up visits. The images will be captured by a Canfield VECTRA H1XP (the “Canfield”).

8.5 FCX-007 Administration to Intact Skin

On Visit 3 (Day 0) and Visit 5 (Week 4), intradermally administer at least 6 0.25 mL injections of FCX-007 to the intact skin per the administration instructions in **Appendix A:Investigational Product Administration Instructions**.

9 Procedures: FCX-007 Administration to Wound(s)

9.1 Selection

A preliminary evaluation of target wounds will occur at the Screening Visit. Potential wounds that meet criteria will be identified at Screening and followed throughout the Wound Monitoring Period. New wounds may also be identified during the Wound Monitoring Period. Final target wound and wound pair selection will occur on Visit 2 based on meeting the following criteria:

1. The total injection area (circumference plus the lengths of the axes) is a maximum of approximately 54 linear cm (see **Figure 4** for more details).
2. If more than one pair of wounds is identified, the sum of the injection areas a maximum of approximately 54 linear cm.
3. If multiple pairs of wounds are identified that meet criteria, wounds with the most consistent wound areas throughout the Wound Monitoring Period are to be selected for the study.

If no wound meets criteria 1 and 2 above, a smaller region of a larger wound may be selected for treatment if it can be matched to a similar area of a larger wound as the control. When selecting a smaller region appropriate for treatment, every effort should be made to minimize the border between the treated and the untreated regions of the wound (See **Figure 6B**). Ideally, a narrow peninsula off the main portion of the wound should be selected for administration of FCX-007.

9.1.1 Location and Condition of Wounds

Wounds located on a mucous membrane or covering facial areas are not permitted and wounds with active infection are not permitted. There are no restrictions regarding proximity of paired wounds.

Wounds should appear clean with adequate granulation tissue, excellent vascularization, and not appear infected. Wounds with evidence of active infection are not eligible. Wounds may be debrided, at the discretion of the Investigator, if there is significant crusting or fibrinous debris.

Bacterial cultures will be obtained from potential target wounds on Visit 2 and as needed based upon standard of care and medical judgment of the Investigator.

9.1.2 Pairing and Labeling of Selected Wound Pairs

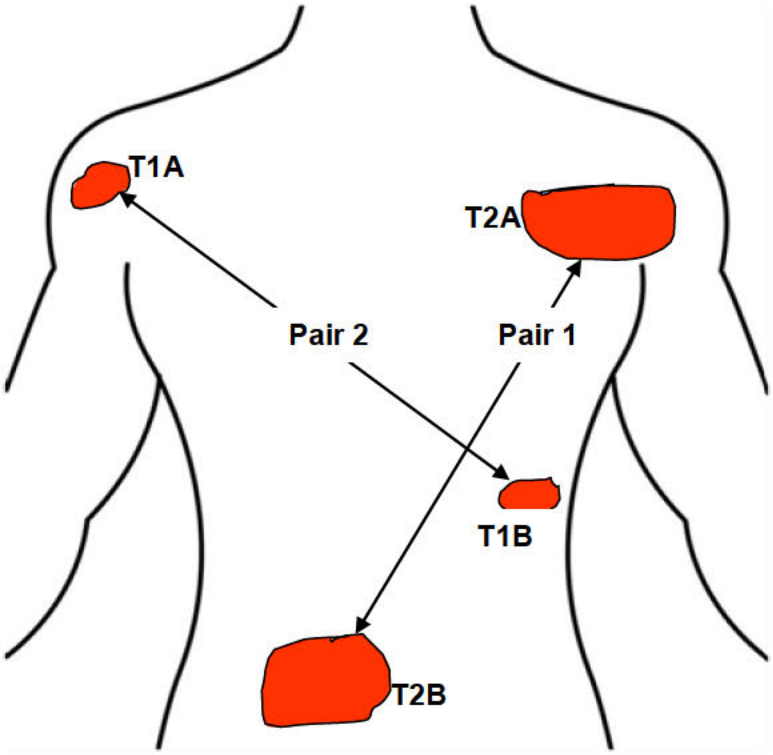
Potential target wounds will be identified by a continuous sequential numbering of Pair 01 (P01) through Pnn. Depending on the size of the largest wound in the pair, the investigator may select up to three pairs of wounds for inclusion in the study. Because the Investigator will not know which of the two paired wounds will be randomly assigned to receive FCX-007, it should be assumed that the largest of the two wounds will receive FCX-007 when calculations are made to determine

how many wound pairs to select. The final selected target wound pairs will be labeled as T1A and T1B for the 1st pair, T2A and T2B for the 2nd pair, and T3A and T3B for the 3rd pair.

The pairs should be ordered from smallest to largest; T1A and T1B will have the smallest injection area, T2A and T2B will have the next smallest injection area, etc. On the day of administration, the smallest wounds will be injected first, the second smallest second, etc.

Figure 4 provides an example and sample calculations for a subject in which two pairs of wounds are selected for inclusion in the study. As shown in the example below, if more than one pair of wounds is identified, the sum of the injectable areas of the largest wounds in the pair must be less than or equal to 54 linear cm. Wounds should be selected with the intent to administer investigational product to the entire injectable area of the target wounds.

Figure 4 - Wound Pairing and Selection Calculations Example



Calculate the injectable areas of potential target wounds

Pair 1
Wound A: Circumference + axes = 12 cm
Wound B: Circumference + axes = 14 cm

Pair 2
Wound A: Circumference + axes = 14 cm
Wound B: Circumference + axes = 10 cm

Add the injectable areas of the two larger wounds of the pair to ensure that they do not exceed 28 cm

Pair 1, Wound B (14 cm)
+
Pair 2, Wound A (14 cm) =

28 cm ✓

9.2 Treatment Assignment of Paired Wounds

Paired wounds will be randomly assigned to receive FCX-007 or no treatment.

On Visit 2, during the selection of the target wounds, each wound of up to three target wound pairs will be labeled by the investigator as T1A and T1B for the 1st pair, T2A and T2B for the 2nd pair, and T3A and T3B for the 3rd pair. Following the determination of target wound pairs, the Investigator will assign each wound to either active treatment or no treatment randomly.

9.3 Imaging / Wound Measurement

Target and control wounds will be measured at each indicated visit using the images captured by a Canfield VECTRA H1XP (the “Canfield”). This Canfield handheld imaging system allows for 3D imaging of skin surfaces. The Canfield software offers a comprehensive set of viewing and measurement tools which allow stitching of multiple images into a 3D image as well as allowing calculation of wound perimeter, linear distances and surface area. Investigators will use a restricted set of tools from the software to define both the perimeter and the wound axes for measurement. The software will provide calculations for investigator evaluation of wounds to select for inclusion in the study.

Prior to the first administration of IP, small tattoos will be placed on non-blistered skin near target wounds for the purpose of calibrating the images.

9.3.1 Investigator Assessment of Wound Healing

The investigator will assess wound healing of target wounds (treated and control/untreated) based on the digital images of the target wounds. The investigator will assess wound healing of target wounds from 0% to 100% healed on a categorical scale. The wound healing assessment will be captured in the following categories.

- 0%
- 1-9%
- 10-24%
- 25-49%
- 50-74%
- 75-89%
- 90-99%
- 100%

9.4 FCX-007 Administration

9.4.1 Preparation

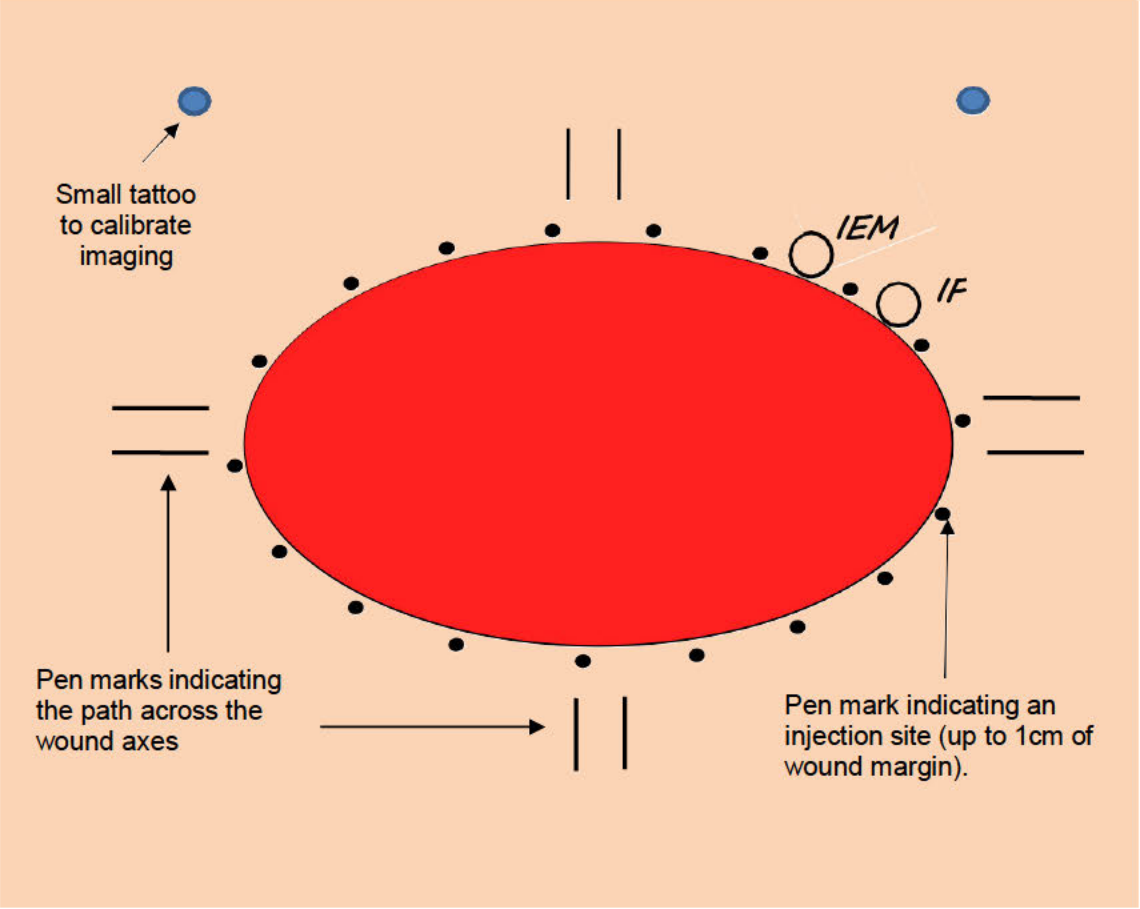
A surgical marker will be used to make the following marks:

- Dots at the injection sites around the periphery of the wound at 1 cm intervals
- Two lines, 1 cm apart, perpendicular from the wound margin, indicating the path of injections across the axes.
- Two circles indicating the location of the IF/DIF and IEM biopsies

Figure 5 provides a diagram of a target wound with markings. After the markings are in place, the wound will be imaged and biopsies obtained.

Prior to the first administration of IP, small tattoos will be placed on non-blistered skin near target wounds for the purpose of calibrating the images. Topical anesthetic cream will be removed from the treatment area prior to treatment. The treatment area will be cleansed with antiseptic solution.

Figure 5 – Sample Drug Administration Preparation Wound Markings



9.4.2 Administration

Reference **Appendix A: Investigational Product Administration Instructions** for detailed instructions regarding the administration of investigational product.

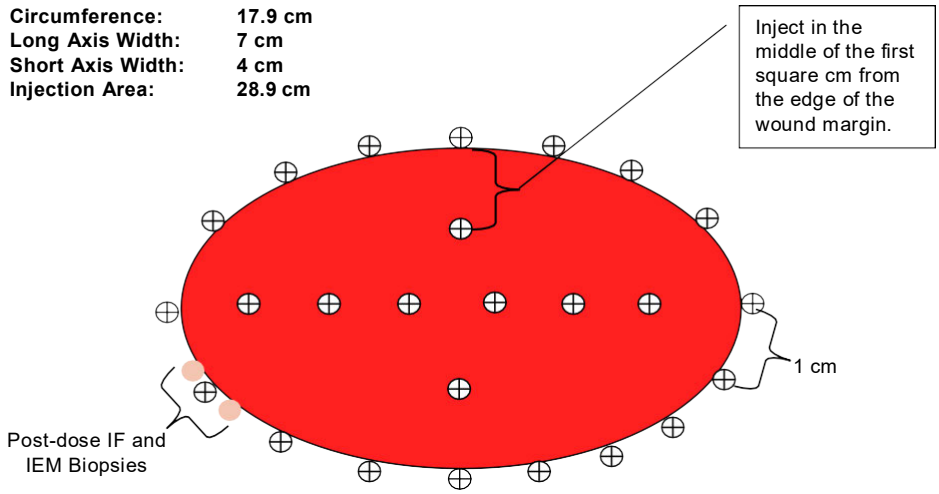
Investigational product is administered intradermally at 1 cm intervals around the periphery of target wounds. The intradermal administration must occur up to 1.0 cm of the wound margin and be administered into the mid-to-superficial dermis. Investigators are to administer 0.25 mL per injection. **Figure 6** provides a graphical depiction of an example target wound showing injection sites and biopsy locations. Locations are shown for (A) treatment of an entire wound, and (B) treatment of a region of a large wound.

9.4.2.1 Treatment of Partial Wounds

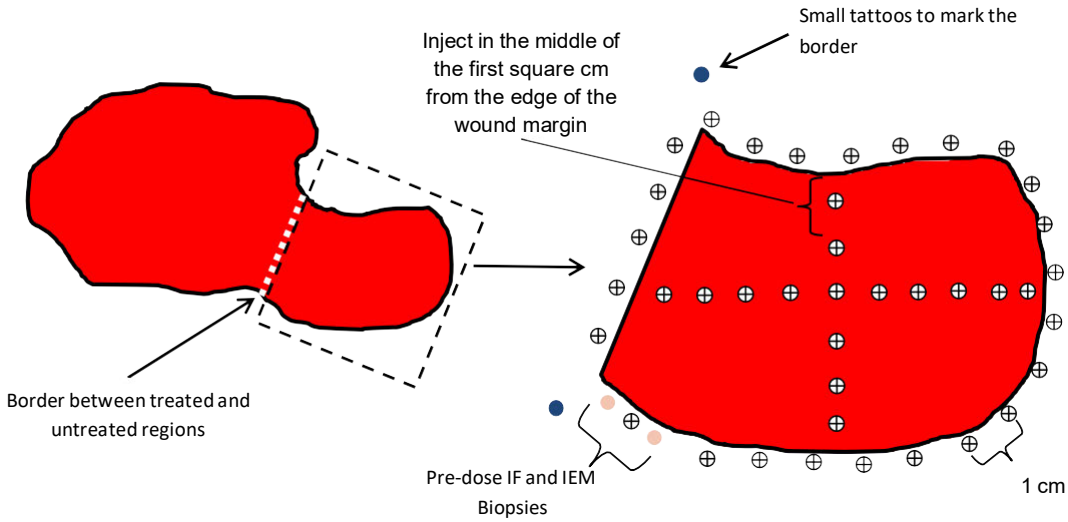
It is preferable to inject whole wounds and not partial wounds; however, partial wounds should be used if whole wounds that meet criteria are not available.

Figure 6 – Example Target Wound, Injection Sites and Biopsy Locations

A: Treatment of an Entire Wound



B: Treatment of a Partial Wound



9.4.3 Visit 5 Administration

Target wounds are administered investigational product up to two times throughout the treatment period; once at Visit 3 (Day 0) and again at Visit 5 (Week 4).

10 Procedures: Collection and Evaluation of Biopsies

10.1 Collection

Biopsies are collected according to **Table 2 - Schedule of Events**. Biopsy handling and shipping instructions are provided in **Appendix B: Biopsy Collection Procedures**. Unscheduled biopsies or laboratory tests may be performed as necessary to evaluate inflammation, possible SCC growths, or suspected presence of C7/anchoring fibrils (wound healing).

At Visits 5 (Week 4), 6 (Week 12), 8 (Week 25) and 10 (Week 52), up to four (4) and a minimum of three (3) biopsies will be collected:

- Two (2) biopsies from intact skin
  - One for IF and DIF analysis to evaluate
    - C7 expression (IF)
    - C7 antibodies (DIF)
  - One to evaluate C7 mRNA and DNA
- One (1) from the target wound to evaluate C7 mRNA and DNA

At other Visits the Investigator may collect up to six (6) biopsies per visit.

The number and type of biopsies obtained will ultimately depend on the judgment of the Investigator and Sponsor.

10.1.1 Collection Location

At all follow-up visits, biopsies are to be collected as closely to the injection sites as possible. To aid in locating the injection sites, a transparent overlay of the injection sites can be generated from imaging which can be placed over the subject's wound / intact skin. Through use of the transparent overlay, aligned with the wound /intact skin according to the tattoos, biopsy sites are chosen that are in alignment with the injection sites. If more than one pair of wounds is included in the study, the target wound from which a biopsy is obtained may vary from visit to visit, at the discretion of the Investigator, to minimize subject discomfort.

10.1.2 Biopsy Photographs and Markings

Biopsy locations around wounds are to be marked with a small circle. The markings will be photographed prior to collection (reference **Figure 5** for a depiction of biopsy wound markings). Biopsy location and purpose will be recorded in the source documentation.

10.2 Evaluation

10.2.1 Immunofluorescence (IF)

Expression of C7 is analyzed at Visits 3 (Day 0), 5 (Week 4), 6 (Week 12), 8 (Week 25) and 10 (Week 52). Skin biopsies may also be obtained at unscheduled visits to evaluate C7 per investigator discretion. A qualified reader will evaluate production of C7.

10.2.2 Immunoelectron Microscopy (IEM)

Expression of C7, both NC1 and NC2 epitopes, and the formation of anchoring fibrils are analyzed through IEM at Visits 3 (Day 0), 8 (Week 25), and 10 (Week 52). Skin biopsies may also be obtained at unscheduled visits. A qualified reader will score the presence of anchoring fibrils. as + (presence of mature anchoring fibrils) or – (absence of mature anchoring fibrils).

10.2.3 DNA Retention and mRNA Expression

At least one skin biopsy is obtained at Visits 5 (Week 4), 6 (Week 12), 8 (Week 25), and 10 (Week 52) to evaluated for genomic retention of C7 proviral vector sequences (DNA retention) as well as mRNA expression.

10.2.4 Autoimmune Assays

C7 Antibodies will be assayed by direct immunofluorescence (DIF) at Visits 3 (Day 0), 5 (Week 4), 6 (Week 12), 8 (Week 25) and 10 (Week 52). Skin biopsies may also be obtained at unscheduled visits per investigator discretion. If there is an autoimmune reaction to C7 then injected fibroblasts may also stain positive for immune reactants. In addition, a Western Blot assay may be performed to complement the indirect and direct IF assays.

The overall assessment of anti-C7 product immune response will be based on each of these assays.

11 Procedures: Safety Assessments

Timing of safety assessments must be performed in accordance with **Table 2 - Schedule of Events**. Safety assessments include evaluation of medical and medication history, physical / skin examination, vital signs, AEs, and laboratory evaluations. AEs will be captured between visits through use of an Adverse Event Diary. Post-administration changes in these assessments that are deemed to be clinically significant by an Investigator or Sub-Investigator will be assessed as AEs.

11.1 Data Safety Monitoring Board

A DSMB comprised of the Medical Monitor, enrolling PIs, and Sponsor representatives and/or designee(s) will hold periodic teleconferences to evaluate the safety and treatment status of all subjects available during the study at these stages:

- After the first subject, prior to the treatment of a second subject in each arm
- After Visit 5 (Week 4) for the third subject, prior to treatment of the first Phase II subject, to make a recommendation as to whether: 1) treatment of adult patients in Phase II of the protocol should continue; and 2) the study should proceed with the enrollment and treatment of children in Phase II of the protocol.

- At any other time as needed

The DSMB has the authority to recommend dose or regimen modifications for safety concerns.

A written summary documenting the results and recommendations of each review will be provided to the investigator(s) and maintained on file with the Sponsor. Additional sub-investigators and scientific personnel may participate in reviews, as appropriate.

The DSMB 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 participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

A DSMB charter will dictate procedures, responsibilities, membership, data requirements and meeting timing.

11.1.1 Stopping Criteria

An objective of this study is to generate a safety profile of FCX-007 in subjects with RDEB. Subjects with RDEB have a significantly increased risk of experiencing SAEs such as serious infections relative to the general population; therefore, in most cases, possible discontinuation of the study will be reviewed on a case-by-case basis. Events which will not be reviewed case-by-case 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. To minimize risk, cumulative safety data will be reviewed by the Medical Monitor and DSMB, as outlined in Section **11.1**.

Occurrence of any of these observations will trigger a temporary suspension of FCX-007 administration pending a safety investigation:

1. A treatment emergent serious adverse event or suspected serious adverse event related to FCX-007, the FCX-007 administration procedure, or any other protocol procedure.
2. A positive RCL qPCR assay result. A positive RCL qPCR assay will result in suspension of FCX-007 administration. The result will be confirmed by conducting a biological-based assay. If both assays are positive, FCX-007 administration will be discontinued and no further enrollment into the study will be allowed.
3. An autoimmune response determined by the Investigator to be possibly, probably or definitely related to treatment.
4. Any systemic infection designated as suspected to be related to FCX-007.
5. A treatment emergent uncontrolled bacterial, viral, or fungal infection in a wound that was administered by investigational product where product sterility testing results reported post injection were positive for contamination.
6. 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.

For subject safety, investigators should continue to follow patients 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 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.

11.1.2 Transition from Phase I to Phase II

The DSMB will review all data through Visit 5 (Week 4) for the first three subjects in each arm of

Phase I of the protocol and make a recommendation as to whether: 1) treatment of adult (≥ 18 years old) patients in Phase II of the protocol should continue; and 2) the study should proceed with enrollment and treatment of children in Phase II of the protocol. The DSMB will consider cumulative safety data, including adverse events, pertinent laboratory and clinical data in making its recommendation to proceed with treatment of adult subjects in Phase II of the protocol. In addition, the DSMB will also consider evidence of direct benefit (see Section **10.1.2.1**) in making its recommendation to proceed with for enrollment of pediatric (aged 7 to 17 years old) subjects in Phase II. Adult subjects will be allowed treatment in Phase II of the protocol upon obtaining the DSMB recommendation to proceed with their treatment. Pediatric patients will only be allowed to enroll into Phase II of the protocol if the DSMB recommends proceeding with enrollment of pediatric subjects into Phase II of the protocol and the FDA provides approval for proceeding to pediatric subjects.

11.1.2.1 Criteria for the Evidence of Benefit

Evidence of benefit is defined as having any one or more of the following three criteria in a single FCX-007 treated wound:

- An increased presence of C7, defined as an increase of 1 or more, relative to baseline, on a biopsy evaluated by immunofluorescence (IF), as measured by a qualified reader.
- The presence of mature anchoring fibrils as designated by a qualified reader.
- Increase in wound healing based on investigator assessment relative to baseline (Day 0) in any wound administered FCX-007.

11.2 Medical and Medication History

The Investigator or delegated staff performs a complete medical history at Screening, including a medication history. The Investigator or staff must record all clinically or medically relevant information. Medical and medication history are reviewed and updated at visit 2 and visit 3.

Select medical history is also reviewed during Prescreening per the process outlined in Section **7.1.1 (Prescreening)** above. The medical history will include respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric and other diseases.

11.3 Physical Examination

A qualified individual will perform a full physical examination Visit 1, 3, and Visit 10. Body systems evaluated will include:

- General appearance
- 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-007 administration), an adverse event form must be completed. In addition, resolution of any abnormal findings during the study will be noted in the source document and appropriate CRF if clinically significant.

11.4 Skin Examination

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-007 administration, attempts will be made to collect samples of the skin cancer to evaluate cells for the presence of viral vector.

11.5 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.

11.6 Laboratory Evaluations

11.6.1 Serum Chemistry and Hematology

Whenever possible, the amount of blood collected should be minimized. Serum chemistry and hematology laboratory analyses will occur locally. 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 the Day -2 lab results will be recorded as an AE if deemed clinically relevant by the Investigator or medically qualified designee. The following evaluations will be conducted:

Serum Chemistry / Metabolic Panel

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

Hematology / Complete Blood Count with Differential

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

11.6.2 Urine Pregnancy Test

A urine pregnancy test will be performed at the Visit 1 and Visit 2 for women of childbearing potential.

11.6.3 Replication Competent Lentivirus Analysis

A replication competent lentiviral (RCL) assay will be performed on 5 mL of blood collected at Visit 1 (at any time up until 4 weeks prior to the scheduled administration date) and Visits 5, 6, 8, and 10, (collected at Visit 7 and 9 if visit is conducted in office) and then yearly thereafter for up to 15 years (as described in the Long-Term Follow-Up Section **7.5**). If all post-treatment RCL assays are negative during the first year (e.g., Weeks 4, 12, 16, 25, 32, and 52), collection of the yearly follow-up samples will be discontinued. The Long-Term Follow-Up blood samples can be collected remotely by the Subject's primary EB care physician. A positive RCL assay result must be recorded as an adverse event.

11.6.4 C7 Antibody Assay

Subject serum will be collected at Screening and Visits 5, 6, 8, and 10 (collected at Visit 7 and 9 if visit is conducted in office) for the purpose of conducting a C7 antibody assay. Subject serum will be evaluated by indirect IF using monkey esophagus as a substrate. Western blot analysis

can be performed as needed. A positive C7 antibody assay result must be recorded as an adverse event.

12 Procedures: Optional Diagnostic Assessments

The following procedures, specific to confirming a subject's diagnosis of RDEB, are performed only under the condition that they have not been conducted and documented previously as determined during Prescreening. If needed, the following procedures are conducted during the Screening Visit.

12.1 Evaluation of Diagnostic Biopsies

If not conducted previously, two biopsies are obtained during the Screening Visit for the purpose of conducting IF and IEM evaluations as outlined in Sections **10.1** and **10.2.2**.

12.2 Genetic Testing

This process is only applicable to potential subjects which are eligible for the study but do not have genotype information. Genetic testing is conducted on the subject to confirm that the subject has RDEB as well as for determination of NC1 status.

The subject is asked to have a blood sample drawn in a laboratory that is convenient for them. This blood sample will be sent to an outside lab for genetic testing. All fees associated with this genetic testing are reimbursed.

12.3 Autoimmune Assay

If not conducted previously, a biopsy is obtained during the Screening Visit for the purpose of performing DIF. Reference Section **10.2.4 Autoimmune Assays.**

13 Adverse Experiences

13.1 Definitions

13.1.1 Adverse Events

An **Adverse Event** (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. 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.

Subjects should be asked a non-leading question in order to avoid bias in eliciting AEs; such as “How are you feeling?” 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. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made then each symptom should be listed individually.

Each AE requires a complete description including date of onset and corrective actions taken. The intensity of the AE and its relationship to the investigational product, as well as its outcome, must be recorded in the CRF.

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 of the symptoms 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 relevant (as determined by the Investigator) or if, during treatment with the investigational product, 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 investigational product, 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 a subject, whether a change in a laboratory parameter represents an AE. For pathological laboratory values that were not present at baseline, follow-up laboratory evaluations should be performed until the values return to within reference range or until a plausible explanation is found.

AEs should be recorded, starting from subject enrollment (date of signature on informed consent) per the Schedule of Events, until the end of the Long Term Follow-Up Period, and are to be recorded on the appropriate AE pages in the CRF and in source documents. Where possible, all AEs should be followed to resolution, or an outcome is reached. Medical tests and examinations will be performed, as appropriate, to document resolution of event(s).

NOTE: Blistering MUST be noted as an AE if it is seen proximal to a product-treated wound.

13.1.2 Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Is fatal.
- Is life-threatening (places the subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Is a persistent or significant disability/incapacity, or
- Is a congenital abnormality/birth defect.

A hospitalization meeting the regulatory requirement for the “serious” criteria is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility.

Any event that does not exactly meet this definition yet, in the investigator’s opinion represents a significant hazard can be assigned the “other significant hazard” regulatory reporting serious criteria.

Additionally, important medical events that may not be immediately life threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the outcomes listed above, or result in urgent investigation, may be considered serious. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

SAEs will be collected and reported throughout the study duration beginning with enrollment through the end of the Long-Term Follow-Up period. If early termination of study treatment occurs, SAEs will continue to be collected until the event resolves.

13.2 Reporting Procedures

All adverse events occurring after FCX-007 administration observed by the investigator or reported by the subject (whether or not attributed to investigational product), will be reported on the case report form.

Medically significant adverse events considered related to the investigational product by the investigator or the sponsor will be followed until resolved or considered stable. The investigator must assign the following attributes: description; dates of onset and resolution; severity; assessment of relatedness to investigational product, and action taken. The investigator may be asked to provide follow-up information.

All deaths occurring on study must be reported to Fibrocell. These include deaths during the Long-Term Follow-Up period. For all deaths, available autopsy reports and relevant medical reports should be provided to the Medical Monitor.

The investigator should notify the IRB of serious adverse events occurring at the site and other

adverse event reports received from Fibrocell, in accordance with local procedures.

It will be left to the investigator's clinical judgment whether or not an adverse event is of sufficient severity to require the subject's removal from study. A subject may also voluntarily withdraw from study due to what he or she perceives as an intolerable adverse event. If either of these occurs, the subject will be asked to undergo an early termination assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable. If the subject was permanently withdrawn from the study due to a serious adverse event, this information must be included in either the initial or follow-up Serious Adverse Event Report Form, and in the End of Study Case Report Form.

The severity of toxicities will be assessed on the following scale with appropriate clinical definitions: Grade1 = mild adverse event, Grade 2 = moderate adverse event, Grade 3 = severe adverse event, Grade 4 = immediate life threatening adverse event, and Grade 5 = fatal adverse event.

The relationship of adverse events to the investigational product will be assessed by the investigator using good clinical judgment according to the following definitions:

- Unrelated: no temporal association or the cause of the event has been identified, or the study drug cannot be implicated based upon available information.
- Unlikely (related): a potential relationship between study drug and the event could exist (i.e., the possibility cannot be excluded), but the event is most likely explained by causes other than the study drug.
- Possible/Possibly (related): temporal association, but other etiologies are likely to be the cause. However, involvement of the study drug cannot be excluded based upon available information.
- Probable/Probably (related): the event and use of study drug are temporally related, and the event is more likely explained by study drug than by other causes.
- Definite/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.

13.2.1 Post-FCX-007 Administration Adverse Event Monitoring

The Investigator must monitor the subject's wounds closely for additional blister formation and expansion of the border of the wound during injections and immediately post-administration up to the 2 day follow up visit. Additional blister formation and/or expansion of the border of the wound must be recorded as an adverse event.

13.2.2 SAE Reporting Procedures

All serious adverse events must be reported to Fibrocell or designee within 1 working day of the earlier of discovery or notification of the event throughout the duration of the study. Initial serious adverse event information and all amendments or additions must be recorded on a Serious Adverse Event Report Form and faxed or emailed to Fibrocell or designee.

14 Statistical Considerations

The objectives of this protocol are outlined in Section **2.2 (Objectives)**.

Treatment visits in this study will include Visits 3 through 10, and unscheduled visits. For efficacy evaluation, the end-of-treatment (or treatment endpoint) will also be defined as a post-treatment assessment time point for efficacy evaluations in order to handle the issue of missing data that is caused by incomplete data collection or early terminations.

14.1 Number of Subjects

A formal sample size calculation was not performed for this study. The sample size is based on what was considered an adequate number of subjects for a pilot study to obtain sufficient information on the safety and effectiveness of FCX-007.

14.2 General considerations

Data will be summarized by treatment regimen and, when applicable, by study visit. Descriptive statistics (number and percentage for categorical data, mean, median, range, standard deviation and N for continuous data) will be presented for each evaluable parameter for change from baseline as well as the value at each timepoint. For discrete variables, descriptive analyses will be based on numbers of subjects (or wounds) and related percentages.

All listings, summaries, figures, and statistical analyses will be generated using SAS version 9.1 or other validated software. When applicable, statistical comparisons between treatments will account for correlated and/or paired data since the data are comprised of multiple wounds on the same individual. Statistical analyses will be exploratory and performed using 2-sided tests at a Type I error rate of 0.05.

14.3 Data Management

Pre-designed CRFs will be used to collect information for safety and proof of mechanism 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.

14.4 Study Populations

The primary population for an analysis of the proof of mechanism is the Full Analysis Set (FAS)

population. Study populations are defined in the following sections.

14.4.1 Safety Population

This population is defined as all subjects who were administered FCX-007.

14.4.2 Full Analysis Set Population

TheFull Analysis Set (FAS) population includes subjects who were administered FCX-007 who have had at least one paired assessment of the target wound area post-administration.

14.4.3 Per-Protocol Population

The per-protocol (PP) population is defined as all subjects in the FAS population who have had at least one paired assessment of the target wound area post-administration, and completed the protocol as planned.

14.5 Demographic and Baseline Characteristics

The descriptive summaries of subjects' demographic and baseline characteristics will be presented by treatment group for the safety, FAS, and PP populations. 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.

14.6 Proof of Mechanism Analyses

14.6.1 Expression of Collagen VII

Biopsies collected for the purpose of IF will be evaluated for expression of C7. Each biopsy will be scored by a qualified reader. Scores will be evaluated and C7 will be considered to be expressed if an increase from baseline is observed.

Change in score from baseline will be evaluated and reported for each post-treatment visit and treatment endpoint by treatment and study phase and will be compared between treatments for each study phase. These analyses will be performed for both FAS and PP populations.

14.6.2 Immunoelectron Microscopy / Production of Anchoring Fibrils

Biopsies collected for the purpose of IEM will be evaluated for the presence of anchoring fibrils, LH24 and mAb185 antibody staining and C7 expression. Evaluation of each item from each biopsy will be scored by a qualified reader. LH24 and mAb185 antibody staining and anchoring fibrils will be evaluated and considered to be present if a score of + is observed.

The percent of target wounds with a + score for each item evaluated will be reported at each post-treatment visit by treatment for each study phase. For quantitative analysis, the obtained results will be assigned a numeric value of 0 and 1, respectively, for – and +. Change in score from baseline will be evaluated and reported for each post-treatment visit by treatment and study phase and compared between treatments for each study phase. These analyses will be performed for both FAS and PP populations.

14.6.3 Target Wound Area

Dimensions of target wounds (treated and control)/ partial wounds will be obtained using the Canfield VECTRA H1-270 System. Dimensions obtained will include length, width, and area (in cm^2). Change in area and other dimensions from baseline initial target wound identification and between visits will be evaluated.

The healed skin area of the target wounds (treated and control)/ partial wound will be evaluated using photographs by the investigator at each post-treatment visit and by treatment and study phase, and will be compared between treatments for each study phase.

The percent of change in the target wound (treated and control) / partial wound area from baseline will be assessed by the investigator at each post-treatment visit and by treatment and study phase, and will be compared between treatments for each study phase.

The proportion of target wounds (treated and control) / partial wounds achieving complete wound closure (≥ 90%) will be reported at each post-treatment visit by treatment and study phase and compared between treatments for each study phase.

These analyses will be performed for both FAS and PP populations.

14.6.3.1 Investigator Assessment of Wound Healing

The investigator will assess wound healing of target wounds (treated and control/untreated) based on the digital images of the target wounds. The investigator will assess wound healing of target wounds from 0% to 100% healed on a categorical scale. The wound healing assessment will be captured in the following categories.

- 0%
- 1-9%
- 10-24%

- 25-49%
- 50-74%
- 75-89%
- 90-99%
- 100%

14.7 Safety Analyses

All continuous parameters will be summarized using standard summary statistics as appropriate (n, mean, standard deviation, median, minimum, maximum, 25th percentile, and 75th percentile). Summary statistics for categorical variables will include frequency counts and percentages.

Patient demographics and relevant baseline data will be analyzed descriptively. Inclusion and exclusion criteria ensure that participants are suitable for the study. Premature termination will be tabulated and summarized.

14.7.1 Adverse Events

Adverse events will be coded using the MedDRA adverse event dictionary. Safety evaluations will be based on occurred adverse events, laboratory values, vital signs and appearance of C7 antibodies, and RCL. Severities of toxicities will be described using the NCI Common Toxicity Criteria (CTC) grades.

Adverse events will be grouped into pre-treatment adverse events and treatment-emergent adverse events and will be tabulated by preferred terminology and by body system for each study phase. The number of adverse event entries, as well as the number of patients will be reported. Analyses will include tabulation of adverse event type, relationship to FCX-007, seriousness, and severity of adverse events according to CTCAE.

14.7.2 Physical Examinations

Physical examinations at screening and subsequent follow-up visits will be displayed in tabular format displaying number of subjects examined and number and percentage of subjects with abnormalities by physical examination category.

14.7.3 Vital Signs

Vital signs will be listed and summarized by means and SD.

14.7.4 Laboratory Tests

Laboratory test values will be presented in shift tables and by display of changes to baseline.

Evaluations of C7 antibodies and RCL will be done descriptively.

14.8 Interim Analysis

There will be no formal interim analysis. The DSMB will evaluate safety following the first subject of each arm, prior to the fourth subject of each arm, and thereafter annually for the duration of the study.

14.9 Handling of Missing and Incomplete Data

Missing values will be captured as such in the CRF database. No imputation for missing data is planned for efficacy analyses, although different assumptions depending on the analysis, may be explored. Standard clinical monitoring and data management practices will be used to ensure the integrity of data.

15 Regulatory Obligations

15.1 Informed Consent

Before a subject's participation in the trial, the investigator (or designee) is responsible for obtaining written informed consent from the subject or legally acceptable representative (see note below) after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

The acquisition of informed consent should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion (not necessarily an investigator). The original signed informed consent form must be retained in accordance with institutional policy, and a copy of the signed consent form must be provided to the subject or legally acceptable representative.

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

15.2 Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material including the information letters must be submitted to the IRB for written approval. A copy of the written approval of the protocol, informed consent form, and advertising material must be received by Fibrocell before recruitment of subjects into the study and shipment of investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB for all subsequent changes to the above named documents. The investigator should notify the IRB of important deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Fibrocell, in accordance with IRB procedures.

The investigator 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's written continuance of approval must be sent to Fibrocell.

15.3 Pre-Study Documentation Requirements

The investigator is responsible for forwarding the following documents to Fibrocell for review before study initiation from Fibrocell can occur:

- Signed and dated protocol signature page (Investigator's Agreement)
- Copy of approved informed consent form and assent form (for phase II)
- Copy of the IRB approval of the protocol, information letter, consent form, and assent form
- Up-to-date curricula vitae of principal investigator and all co/subinvestigators
- The IRB composition and/or written statement that IRB is in compliance with regulations
- Laboratory normal ranges and documentation of laboratory certification (or equivalent)
- Current subject/investigator indemnity insurance
- Signed study contract
- Completed FDA form 1572. Laboratories providing primary and secondary endpoint data and any central laboratories for the study must be listed on the form.
- For studies covered under 21 CFR Part 54.2(e), "Financial Disclosure," completed Financial Disclosure statements for the principal investigator, all subinvestigators, and their spouses (legal partners) and dependent children.

15.4 Subject Confidentiality

The investigator must take all reasonable measures to ensure that the subject's confidentiality is maintained. On the case report forms or other documents submitted to the study sponsor and those working with the study sponsor, subjects should be identified by their initials and a subject study number only. Documents that are not for submission to the study sponsor and those working with the study 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 Fibrocell and companies that work with Fibrocell, of the regulatory agency(s), 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.

16 Administrative and Legal Obligations

16.1 Protocol Amendments and Study Termination

Protocol amendments must be made only with the prior approval of Fibrocell. Agreement from Fibrocell must be obtained for all protocol amendments and amendments to the informed consent document. The IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the subjects or the conduct of the trial. The investigator must send a copy of the approval letter from the IRB to Fibrocell.

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

16.2 Study Documentation and Storage

16.2.1 Delegation Log

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated trial duties. All persons authorized to make entries and/or corrections on case report forms will be included on the Delegation of Authority Form.

16.2.2 Source Documents

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

16.2.3 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 Fibrocell, companies that work for and with Fibrocell, and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed case report forms, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, investigator's brochure, copies of prestudy documentation, and all correspondence to and from the IRB and Fibrocell
- Proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product

Reconciliation Statement, and all drug-related correspondence

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.

No study document should be destroyed, moved to another location, or assigned to another party without prior written consent of Fibrocell.

16.3 Study Monitoring and Data Collection

The Fibrocell monitor is responsible for inspecting the case report forms at regular intervals to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the case report forms.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing case report forms, are timely resolved.

16.4 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 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.

17 Bibliography

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18 Summary of Changes

Version	Section	Original	Amendment
8.0	Throughout	Visit numbers detailed	Visit numbers with associated timing of study visits in days/weeks, as applicable, specified.
	Throughout	Visit number inconsistencies (Visit 5, Visit 6) when second FCX-007 administration to occur	Visit 5 (Week 4) specified where applicable.
	Background; Investigational Product	FCX-007 to be administered within 40 hours of vial fill time.	FCX-007 to be administered prior to the expiration date and time indicated on the product label.
	Rationale and Objectives	Fibrocell and Intrexon are co-developing FCX-007.	Removed Intrexon as co-developer.
	Rationale and Objectives; Study Design	Efficacy evaluation based on digital imaging system dimensions/calculations.	Efficacy evaluation based on investigator assessment of wound healing based on digital images of wounds.
	Study Design	Assignment of subjects into two arms based on NC1 status in each phase of the study.	Assignment of subjects into two arms based on NC1 status in Phase 1
	Study Design	Enrollment specifications in each arm and phase of the study prior to moving into next phase.	Removed
	Study Design; Investigational Product; FCX-007 Administration	FCX-007 administered around the margins and across the axes of wounds	Removed across the axes of wounds.
	Study Design; Study Visits	Subject target wounds will be imaged during the Wound Monitoring Period.	Subject target wounds may be imaged during the Wound Monitoring Period.
	Study Design; Study Visits; Safety Assessments;	RCL testing to occur annually in Years 1-5 in the LTFU period.	RCL testing to occur yearly in the LTFU period for up to 15 years, however if subject's RCL test results are negative in the first year, further yearly RCL testing will be discontinued.
	Investigational Product; FCX-007 Administration	Sterile saline as investigational product/comparator.	Removed
	Study Design; Study Visits; FCX-007 Administration; Statistical Considerations	N/A	Added investigator assessment of wound healing
	Study Visits	One biopsy from intact skin and wounds for IF	One biopsy from intact skin and wounds for IF and DIF
	FCX-007 Administration	Target wounds measured	Target and control wounds measured
	FCX-007 Administration	Injecting across the bed of target wounds, the injection should be placed midway across the first square cm from the wound margin.	Removed
	Collection/ Evaluation of Biopsies;	Biopsy for IF analysis to evaluate C7 expression	Biopsy for IF/DIF analysis to evaluate C7 expression (IF) and C7 antibodies (DIF)
	Collection/ Evaluation of Biopsies;	N/A	Direct immunofluorescence (DIF) testing also performed on the biopsy collected for immunofluorescence (IF) testing.
	Collection/ Evaluation of Biopsies; Safety Assessments; Statistical Considerations	IF evaluation result details, e.g., Each target wound biopsy is rated as -, +, ++, or +++.	Removed

Version	Section	Original	Amendment
8.0 (continued)	Collection/ Evaluation of Biopsies; Safety Assessments	C7 antibodies by will be assayed by DIF.	Specified visits when expected.
	Collection/ Evaluation of Biopsies;	DIF detailed testing specifications	Removed
	Safety Assessments	DSMB teleconference timing to occur after visit 5 (Week 4) for the third subject, prior to treatment of the first Phase II subject in each arm; and annually from the date of the first subject, first administration.	Removed “in each arm” and annual meeting from the date of first subject, first administration.
	Safety Assessments	Reduction in wound size relative to average area of the wound observed during the Wound Monitoring Period	Increase in wound healing based on investigator assessment
	AE	AE relationship option of yes or no.	AE relationship options revised to unrelated, unlikely, possible/possibly, probable/probably, or definite/definitely related.
	AE	SAE reporting to Fibrocell.	SAE reporting to Fibrocell or designee.
	Statistical Considerations	N/A	Added general considerations section
	Statistical Considerations	Intent-to treat population	Revised to Full Analysis Set population
	Statistical Considerations		Updated to reflect revisions to data being collected and evaluated.
7.0	Study Design	At Week 12 visit, subjects receive second administration in wounded and intact skin.	At Week 4 visit, subjects receive second administration in wounded and intact skin.
6.0	Study Design	Visits are described in Weeks	Aligned Visit numbers to Weeks
	Study Design	12 subjects	Up to 12 subjects
	Study Design	Subjects will receive a second administration at Week 25 if unhealed portions of the target wound remain, and if there is evidence of function (an increase in C7, an increase in anchoring fibrils, or a presence of viral vector or mRNA) at the target wound or in a site of intact skin as determined through biopsy results. A subject may also receive an FCX-007 administration to intact skin at Week 25 if there was evidence of function at the site of intact skin at Day 0.	At Week 12 visit, subjects receive second administration in wounded and intact skin.
	Study Design	The first three (3) visits of the Treatment Period (Day -2 to Day 2) will be scheduled so that the day of dosing (Day 0) is the day of receipt of FCX-007.	The Treatment Period can occur in as few as 2 days and up to 4 days, as safety and schedules permit.
	Number of Injections	Up to 40	Up to 60
	FCX-007 Administration	Inject 0.25cm away from the wound margin	Inject up to 1cm away from the wound margin
	Dose volume	[redacted]	[redacted]
	FCX-007 Administration	Target wound size of 34cm	Increase to 54cm
	Study Design	In Phase II, control wounds treated with saline	In Phase II, control wounds remain untreated

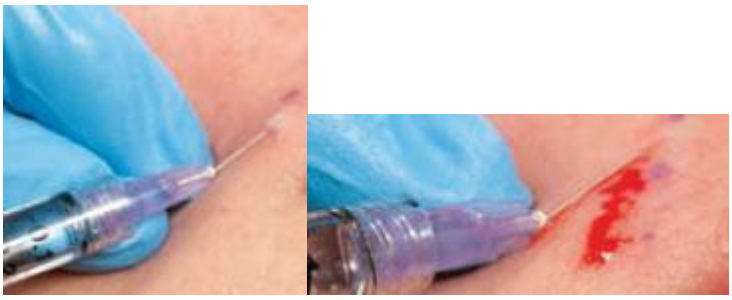
Version	Section	Original	Amendment
6.0 (continued)	FCX-007 Background	The safety and biodistribution of FCX-007 was evaluated in a 3-month toxicology/toxicokinetics study in NSG mice injected subcutaneously with six doses of FCX-007. FCX-007 was well tolerated throughout the 3-month timepoints.	The safety and biodistribution of FCX-007 was evaluated in a 6-month toxicology/toxicokinetics study in NSG mice injected subcutaneously with six doses of FCX-007. FCX-007 was well tolerated throughout the 3 and 6-month timepoints.
	Study Visit		Based on subject safety and scheduling, Visits 7 and 9 may be conducted with the investigator and subject via telephone.
	Study Design	Paired wounds will be randomized via DataTrak to be randomized to treatment or no treatment	Paired wounds will be randomly assigned to treatment or no treatment

Appendix A: Investigational Product Administration Instructions

1. Intradermal injections are to be administered by the Investigator or an appropriately trained delegated health care professional.
2. Administer anesthesia. Subjects will be administered anesthesia per standard of care at the Investigative Site. To minimize pain and discomfort during the investigational product administration, the Investigator should determine the most appropriate anesthetic for each subject, including the use of topical anesthetic cream, local anesthesia, conscious (moderate) sedation, general anesthesia (if undergoing another procedure at time of injection) or a combination thereof. In addition, medication should be considered during and after the injections to treat pain and/or anxiety (i.e. lorazepam).
3. Mark the skin as indicated in Section **8.2** (intact skin) and Section **9.4.1** (wounds).
4. Approximately 15 minutes prior to the administration of FCX-007, 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 the 30-gauge needle for injection of the product. 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 30-gauge needle at the first mark.
11. Introduce the needle into the superficial papillary dermis at 0.25 mL per linear centimeter and bring the needle along a line parallel to the wound margin. The shadow of the needle under the skin must be visible if the injector is in the correct plane. If it is not, replace the needle just adjacent to the initial area of insertion in a more superficial plane.

12. The graduated markings on the syringe should be visible to ensure that the correct amount is being injected.
13. Once the needle is inserted, apply light pressure to the plunger and inject very slowly, injecting very tiny boluses into the treatment area as the needle is withdrawn (the cells must be injected as delicately as possible). Keep a close eye on the amount and the skin to ensure only 0.25 mL is injected into each centimeter, and a wheal is formed with each bolus. Stop injecting before withdrawing the needle and remove your thumb from the plunger.
14. Immediate blanching of the skin or a small wheal must be seen as the product is injected. If the needle is in the superficial (papillary) dermis it will be difficult to inject too much volume. If you see no blanching or wheal when the product is initially injected, reposition the needle in a more superficial plane and inject additional product.
15. Record any seepage of product or immediate impact to overall wound size.

Figure 7 - Photographs of Intradermally Administered Fibroblasts Cells



Appendix B: Biopsy Collection Procedures

Biopsy Supplies

The following biopsy supplies will be supplied to the site as needed:

- Punch biopsy instruments
- Biopsy Transport Vials containing sterile phosphate buffered saline or sterile culture medium such as DMEM
- Associated documentation
- Shipping materials

Prior to the procedure, the surgeon will need to assemble other items required as follows:

- Syringe and local anesthetic and topical anesthetic cream
- Scalpel (optional) for excision of sample from base
- Suture needle (optional)
- Scissors and/or forceps without teeth as desired
- Wound dressing

Collection Procedure

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. The neck, head (with the exception of post-auricular), groin, hands, feet and axilla are excluded areas. Based on previous experience with collecting biopsies from RDEB subjects under IRB approved protocol for product development purposes, the anatomical locations including upper leg, calf, trunk and upper arms (in descending order of frequency) are recommended areas.

- Anesthetize the area by topical anesthetic, local perfusion.
- Prepare the area.
- 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.
- Gently place excised tissue into cryovial using forceps.
- Close donor site as appropriate.
- Complete associated biopsy inventory form with appropriate subject information.
- Package and ship biopsy as described in the Study Procedures Manual.

Local Anesthesia

All biopsies are obtained after anesthesia. All anesthesia medication must be recorded on the concomitant medication source documents and CRF pages. Investigative sites should employ standard practice to locally anesthetize the biopsy areas. It is anticipated that a topical lidocaine or lidocaine / prilocaine cream will be followed by a 1% lidocaine with epinephrine (10 mg/mL with epinephrine) injection.