CLINICAL STUDY PROTOCOL

Title:	A Pivotal Phase 3 Study of FCX-007 (Genetically-Modified Autologous Human Dermal Fibroblasts) for Recessive Dystrophic Epidermolysis Bullosa (DEFI-RDEB)
Protocol Number:	FI-EB-002
Sponsor:	Castle Creek Biosciences, LLC 405 Eagleview Boulevard Exton, PA 19341
Investigational Product:	FCX-007 (D-Fi)
Development Phase:	3
Protocol Version / Date:	Version 5.1, 04-MAY-2022

GCP Statement

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

SPONSOR PROTOCOL APPROVAL

Title:	A Pivotal Phase 3 Study of FCX-007 (Genetically-Modified Autologous Human Dermal Fibroblasts) for Recessive Dystrophic Epidermolysis Bullosa (DEFI-RDEB)
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This protocol has been approved by Castle Creek Biosciences, LLC (Castle Creek).

DocuSigned by:
[redacted]
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5/4/2022
Date

[redacted]
Chief Medical Officer

1. INVESTIGATOR'S AGREEMENT

Title:	A Pivotal Phase 3 Study of FCX-007 (Genetically-Modified Autologous Human Dermal Fibroblasts) for Recessive Dystrophic Epidermolysis Bullosa (DEFI-RDEB)
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I have read and understood the contents of the above referenced protocol.

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

Principal Investigator's Name (Printed)

Principal Investigator's Signature

Date

2. SYNOPSIS

Sponsor: Castle Creek Biosciences	**Protocol Number:** FI-EB-002
Protocol Title: A Pivotal Phase 3 Study of FCX-007 (Genetically-Modified Autologous Human Dermal Fibroblasts) for Recessive Dystrophic Epidermolysis Bullosa (DEFI-RDEB)	
Investigational Product: FCX-007 (D-Fi)	**Phase of Development:** Phase 3

Objective:

The primary efficacy objective is to determine whether administration of FCX-007 in addition to standard of care improves wound healing as compared to standard of care alone (control) in children, adolescents, and adults with Recessive Dystrophic Epidermolysis Bullosa (RDEB) and confirmed mutation of the type VII collagen gene (COL7A1) gene.

Methodology:

DEFI-RDEB is a multi-center, intra-patient randomized and controlled, open-label, Phase 3 study of FCX-007 for the treatment of RDEB wounds. FCX-007 is comprised of autologous fibroblasts isolated from the RDEB subject's skin biopsies and transduced with a virus containing the full-length COL7A1 gene to produce functioning type VII collagen (COL7).

Up to three target wound pairs, comprised of 10-50 cm^2 wounds (5-50 cm^2 for subjects 2 to 6 years of age at time of consent), will be identified for each subject. The Investigator will assign a First (Primary) Pair for primary endpoint evaluation, additional applicable pairs will be designated as Second (Secondary) and Third (Tertiary) Pairs. Following pairing, target wounds will be randomly assigned as the treatment wound (FCX-007 is administered) or control wound.

Subjects will receive intradermal injections of FCX-007 in each specified treatment wound in two or more treatment sessions. The first treatment session occurs at Day 1 (Visit 2) and the second at Week 12/Month 3 (Visit 3). Additional treatment sessions may occur at Week 24/Month 6 (Visit 4) and Week 36/Month 9 (Visit 5) when unclosed treatment wounds may be re-treated, and unclosed control wounds may be treated. Intradermal injections of FCX-007 0.25 mL per linear centimeter are administered around the perimeter and across each wound bed; a maximum of 15 mL may be administered per session.

Safety and efficacy assessments will occur at scheduled intervals through Week 48/Month 12 (Visit 6), when the treatment period is completed, and a long-term safety (with optional efficacy) follow-up period (through 15 years) commences for subjects who have received one or more FCX-007 injections of any volume.

Number of Subjects (Planned):

Up to 40 subjects may be screened to ensure a minimum of 24 evaluable subjects for the primary efficacy endpoint.

If applicable, subjects treated in other clinical studies of FCX-007 may be enrolled in the long-term safety follow-up period.

Number of Study Centers (Planned):

Approximately 4-6 investigative sites in North America.

Diagnosis and Main Criteria for Inclusion:

Male or female subjects ≥2 years of age with a confirmed diagnosis of RDEB.

Expected Duration of Subject Participation: approximately 16-18 months for primary safety and efficacy period; approximately 15.5 years for long-term safety follow-up period

- Screening Period (minimum 12-week Wound Monitoring Period, FCX-007 manufacturing) has an expected duration of approximately 4-6 months.
- Treatment Period includes FCX-007 administration at Day 1 (Visit 2) and Week 12/Month 3 (Visit 3) to the treatment wound(s) only. FCX-007 may also be administered at Week 24/Month 6 (Visit 4) and Week 36/Month 9 (Visit 5) to unclosed treatment wounds and unclosed control wounds, per the investigator's discretion.
- An End-of-Treatment visit occurs at Week 48/Month 12 (Visit 6).
- Subjects who receive at least one FCX-007 administration will continue in a Long-Term Safety Follow-up Period through 15 years.

Investigational Product: FCX-007 (autologous fibroblast cells, 1.0 – 3.0 x 10^7 cells/mL)

Mode of Administration: Intradermal

Dose: 0.25 mL injections; a maximum of 15 mL may be administered per treatment session

Reference Product:

None; standard of care therapy will be permitted.

Criteria for Evaluation:

Efficacy: Complete wound closure (investigator assessment), durability of response (complete wound closure), change in surface area of wound (image analysis), pain in wounds (patient reported outcome, Wong-Baker FACES® Pain Rating Scale, ages 3 and older). The expression of COL7 in treated wounds will be assessed by immunoelectron microscopy (IEM) and immunofluorescence (IF) in a subset of subjects.

Safety: Adverse events (AEs), vital signs, physical and skin examinations, clinical laboratory testing, replication-competent lentivirus (RCL) testing, antibody response to COL7, neoplasms (squamous cell carcinoma (SCC) or sarcoma) and/or inflammation.

Statistics:

Primary efficacy endpoint:

- Complete wound closure of the First Wound Pair at Week 24

Secondary efficacy endpoints:

- Complete wound closure of the First Wound Pair at Week 12
- Complete wound closure of all wounds at Week 24
- Complete wound closure of all wounds at Week 12

Supportive efficacy endpoints:

- Durability of wound closure from Week 24 through Week 48
- Durability of wound closure from Week 24 through Week 36
- Durability of wound closure from Week 12 through Week 48
- Durability of wound closure from Week 12 through Week 36
- Change from baseline in surface area of each wound at Weeks 12, 24, 36, and 48
- Change from baseline in Wong-Baker FACES Pain Rating Scale at Weeks 12, 24, 36, and 48
- COL7 expression in a treated wound as assessed by IEM and IF at Weeks 36 and 48

Statistical Considerations:

Based on observed Phase 1/2 study data, 60% wound closure in treated wounds, and 10% wound closure in control wounds is assumed, with a total discordance of 70%. A sample size of 24 provides 85% power at a significance level of 0.05 to detect a difference of 50% between treated and control wounds when there are 70% discordant pairs, using a McNemar's test.

Safety:

Safety evaluations will be based on AEs, vital signs, laboratory values, RCL, antibody response to COL7, neoplasms (SCC or sarcoma) and/or inflammation. Severities of AEs will be described using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grades. AEs will be coded and tabulated using the Medical Dictionary for Regulatory Activities and summarized by body system and preferred term. Incidence of AEs will be presented overall, by system organ class, and preferred term. Analyses will include tabulation of AE type, relationship to FCX-007, seriousness, and severity of AEs according to CTCAE. AEs causing investigational product discontinuation and/or early study discontinuation and incidence of serious adverse events will be summarized.

Laboratory test values will be presented in shift tables and by display of changes to baseline. Evaluations of COL7 antibodies and RCL will be done descriptively.

Vital signs will be listed and summarized by means and standard deviation (SD).

Efficacy:

The primary population for analysis of efficacy is the full analysis set (FAS). The FAS population includes subjects who were administered FCX-007.

The primary efficacy endpoint is complete wound closure of the First Wound Pair at Week 24, with confirmed complete wound closure at serial assessments at Weeks 22 and 24. The method of analysis will be logistic regression using a compound symmetry covariance structure.

The first secondary endpoint, complete wound closure of the First Wound Pair at Week 12, will be analyzed similarly to the primary endpoint. The remaining secondary endpoints will be analyzed similarly to the primary endpoint, with consideration of the repeated measurements within subjects.

Testing of the secondary endpoints will follow a gated sequential approach. Once the primary endpoint demonstrates statistical significance, the secondary endpoints will be tested in the given order, with testing of each endpoint proceeding only if the preceding endpoint reaches statistical significance.

Any testing of the supportive efficacy endpoints will be done for exploratory purposes only; no adjustment for multiplicity will be made.

The primary method of handling data will be last observation carried forward (LOCF). Sensitivity analyses will be included in order to assess the impact of missing data.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
abs	Absolute
AE	Adverse Event
AF	Anchoring Fibrils
ALT/SGPT	Alanine Aminotransferase
AST/SGOT	Aspartate Aminotransferase
BLA	Biologic License Application
BMZ	Basement Membrane Zone
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
cm	Centimeter
cm^2	Square Centimeter
COL7	Type VII Collagen
COL7A1	Type VII Collagen Gene
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DEFI-RDEB	A Pivotal Phase 3 Study of FCX-007 (Genetically-Modified Autologous Human Dermal Fibroblasts) for Recessive Dystrophic Epidermolysis
DIF	Direct Immunofluorescence
DMEM	Dulbecco's Modified Eagle Medium
DOB	Date of Birth
DP	Drug Product
DSMB	Data Safety Monitoring Board
EB	Epidermolysis Bullosa
EDC	Electronic Data Capture
EOT	End of Treatment
ELISA	Enzyme-Linked Immunosorbent Assay
FAS	Full Analysis Set
FCX-007	Genetically-Modified Autologous Human Dermal Fibroblasts
FDA	Food and Drug Administration
FISH	Fluorescence *in situ* Hybridization
GCP	Good Clinical Practice
GM-HDF	Genetically Modified Human Dermal Fibroblasts
H&E	Hematoxylin and Eosin

Abbreviation	Definition
HBsAg	Hepatitis B Surface Antigen Screening
Hep B	Hepatitis B
Hep C	Hepatitis C
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigational Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEM	Immunoelectron Microscopy
IF	Immunofluorescence
Ig	Immunoglobulin
IIF	Indirect Immunofluorescence
IND	Investigational New Drug application
IP	Investigational Product
IRB	Institutional Review Board
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mm	Millimeter
NC	Non-collagenous
NCI	National Cancer Institute
PC	Phone Contact
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PP	Per-Protocol
qPCR	Quantitative Polymerase Chain Reaction
RBC	Red Blood Cell(s)
RCL	Replication-Competent Lentivirus
RDEB	Recessive Dystrophic Epidermolysis Bullosa
RDW	Red Cell Distribution Width
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

Abbreviation	Definition
SCC	Squamous Cell Carcinoma
SD	Standard Deviation
SIN #	Subject Identification Number
Sub-I	Sub-Investigator
TEAE	Treatment-Emergent Adverse Events
US/USA	United States of America
WA	Wound Assessment
WB	Western Blot
WBC	White Blood Cell(s)
WHODrug Global	World Health Organization Drug Global Dictionary

4. INTRODUCTION

4.1. BACKGROUND

Epidermolysis bullosa (EB) is a clinically and genetically heterogeneous group of inherited blistering diseases that affect the skin and mucous membranes. The blisters can be in the epidermis, dermis, or junction of dermis and epidermis, the location of which is dependent upon the mutation in at least 18 different genes. The four main types of EB include EB Simplex, Junctional EB, Dystrophic EB and Kindler Syndrome, with additional subtypes identified within each type. EB affects ~500,000 people worldwide and ~5% of affected individuals have the clinically more severe variant, recessive dystrophic epidermolysis bullosa (RDEB) (Rashidghamat, 2017).

RDEB is an autosomal recessive, inherited skin disease caused by mutations within the type VII collagen gene (COL7A1). The COL7A1 gene encodes for the type VII collagen protein (COL7). The mutations cause an absence or reduction of functional type VII collagen protein, the primary component of anchoring fibrils (AFs), in the basement membrane zone (BMZ) between the dermis and the epidermis. Absent or reduced AF function causes separation of the epidermis from the dermis in response to minor skin trauma resulting in mechanical fragility of the skin and recurrent blister formation, potentially occurring on all epithelial-surfaced or lined structures. Heterozygotes (carriers) are typically asymptomatic demonstrating that 50% of normal COL7 is sufficient for skin integrity. It is estimated that 30-50% of "normal" levels of functional COL7 confers resistance of the skin against shearing forces and improves in RDEB (Fritsch, 2008).

RDEB is associated with significant morbidity due to persistent blistering and subsequent scarring on skin surfaces and mucous membranes that substantially impact day-to-day functioning. Fusion of fingers and toes and contractures cause deformity, immobility and loss of function. The list of manifestations and secondary complications requires multiple interventions from a range of medical specialists, and results in disfigurement, disability and in many cases early death. 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 (SCC), sepsis, or of malnutrition due to an inability or unwillingness to eat due to mouth or esophagus involvement (RAC, 2007). No curative treatments exist for RDEB.

The main principle of care in RDEB is to manage blisters and wounds, control infection and prevent complications. Lack of COL7 causes a delay in cutaneous wound healing, increased risk of infection, inflammation, and development of a continuum of chronic wounds with similar biology and physical characteristics, that can be classified as either chronic open wounds that stay open for ≥12 weeks (persistent non-healing wounds) or recurrent open wounds defined as areas that heal but then easily re-blister due to repetitive trauma (Lazarus, 1994; Cianfarani, 2017; Solis, 2017; personal communication Dr. Jean Tang, MD, PhD). Studies have documented the extensive distribution of wounds and show that patients with RDEB generalized severe subtype may have skin wounds on any surface, especially sites exposed to mechanical stress (Cianfarani, 2017). The natural history of wounds in EB study by Solis, et al. demonstrated that persistent non-healing wounds have a duration of ≥7 years and as suggestive of their description, these wounds never heal. In contrast, the majority of recurrent wounds heal within 3 weeks but re-blister/open within 3 weeks (Solis, 2017).

The negative psychosocial impact of chronic wounds in patients with RDEB, and the medical and financial burden of wound care due to chronic wound infections, pain, and pruritus is well documented (Adni, 2012; FDA, 2020; Fine, 2004; Goldschneider, 2014). Optimal treatment of RDEB will likely involve a combination of therapies. Given that the essential skin pathology in RDEB is a lack of COL7 in the basement membrane, Castle Creek has developed FCX-007, an autologous gene and cell therapy product that is intradermally administered and may be used for all RDEB patients, regardless of mutation type, for chronic non-healing and recurrent wounds. The safety and efficacy of FCX-007 is being studied for the treatment of wounds in patients with RDEB.

4.2. STUDY RATIONALE

4.2.1. Clinical Background

FCX-007 has been investigated in one clinical study. This Phase 1/2 open label clinical trial (Study FI-EB-001) assessed the safety, pharmacology and wound healing effect of FCX-007 on RDEB subjects (NCT 02810951).

Six RDEB subjects, five adults (n=8 wounds) aged 20 to 38 years and one child (n=2 wounds) aged 9 years, were dosed with FCX-007. The therapy was administered in the margins of and across targeted chronic persistent non-healing wounds, (ranging in size between 4.4 and 34.1 square centimeter (cm^2)), as well as in separate intact skin sites. Subject demographics are listed in Table 1. Persistent non-healing wounds were targeted to assess the efficacy of wound healing. Intact skin sites were injected to assess mechanism of action. All six subjects received a single intradermal treatment at baseline. Four subjects received a second treatment in the target wound, sequentially decreasing the duration between the baseline and second injection (52, 25, 12, and 4 weeks post-baseline administration, respectively)..

Table 1: Study FI-EB-001 Subject Demographics

Subject #	101	102	103	104	105	106
Age at enrollment	26	21	33	38	33	9
Sex	M	M	M	F	M	M
COL7A1 Mutation 1	5048_5051 dup (GAAA) (exon 54)	5048_5051 dup (GAAA) (exon 54)	6527dupC (exon 80)	356_357 delCA	8440 C>T (homozygous)	1573 C>T
COL7A1 Mutation 2	90delC (exon 2)	90delC (exon 2)	7485 + 5 G>A (intron 98)	2017G>T	8440 C>T (homozygous)	6527dupC
COL7 Expression (IF)	Negative	Negative	Negative	Negative	Negative	Negative
COL7 Expression (WB)	NC-1 positive	NC-1 positive	NC-1 positive	NC-1 negative (null)	NC-1 positive	NC-1 positive
Electron Microscopy	no AF/ sublamina densa split	no AF/ sublamina densa split	no AF/ sublamina densa split	no AF/ sublamina densa split	no mature AF	no AF/ sublamina densa split
COL7 Antibodies	Negative	Negative	Negative	Negative	Negative	Negative
History of SCC	No	No	No	Yes	Yes	No

AF = anchoring fibrils; IF = immunofluorescence; NC-1 = non-collagenous-1; SCC = squamous cell carcinoma; WB = Western blot

4.2.1.1. FI-EB-001 Efficacy Results

Evidence of COL7 expression, full length COL7 formation via non-collagenous (NC)-1 and 2 detection and AF formation has been observed in subjects' samples up to 52 weeks post-administration. In addition to COL7 detection, quantitative polymerase chain reaction (qPCR) analysis of skin biopsy samples shows vector detection up to 25 weeks post-administration of FCX-007, indicating that the cells are still present in skin for at least this timeframe. That FCX-007 vector was detected at least to 25 weeks post-administration is significant since a different clinical study of human male fibroblasts injected into a human female recipient using XY chromosomal probes by fluorescence *in situ* hybridization (FISH) showed no persistence of cells 2 weeks after injection, suggesting that allogeneic cells may not provide a durable response (Wong, 2008). With FCX-007, positive wound closure trends, assessed by investigator impression of wound closure were demonstrated compared to untreated control wounds.

At 12 weeks, 8/10 treated wounds demonstrated complete (or ≥90% closure) wound closure whereas none of the control wounds demonstrated complete wound closure. Of note, this study was not powered to show statistical differences. The duration of wound closure appears to be longer in comparison to allogeneic fibroblasts which demonstrate approximately 4 weeks of wound closure but subsequently breakdown (Petrof, 2013).

4.2.1.2. FI-EB-001 Safety Results

FCX-007 was well tolerated up to 52 weeks post-administration with no antibody response detected after initial or repeat administration.

Three subjects treated with FCX-007 had serious adverse events (SAEs). Two subjects (had SAEs of SCC of the skin, neither in a treated area. One subject's SAE had a fatal outcome; the subject died of SCC progression, approximately 4.5 months following a surgical amputation. SCC is commonly diagnosed in RDEB patients (69%) (Montaudié, 2016; Fine, 2014), and treatment in areas with SCC was prohibited in the study. The SAEs of SCC progression were deemed unrelated to the investigational product (IP) by the investigator and Data Safety Monitoring Board (DSMB). Subject 106 had an SAE of flu with nausea, vomiting, and gastritis that resulted in hospitalization approximately one-month post-FCX-007 treatment that was deemed unrelated to the IP by the investigator.

No stopping criteria was met in the study. All other adverse events (AEs) reported were considered to be unrelated to study treatment, while an event of mild erythema after injection procedure resolved within 1-2 days. No replication-competent lentivirus (RCL) and no COL7 antibody responses have been noted in serum samples from subjects, including one subject with a negative NC-1 genotype.

The Phase 1/2 study indicates that FCX-007 treatment appears to be safe and effective for treatment of RDEB wounds. FCX-007 gene/cellular therapy may improve wound healing and may benefit RDEB patients, regardless of mutation type, for chronic persistent non-healing and recurrent wounds. Based on the favorable risk/benefit outcomes to date, this Phase 3 study will be conducted to confirm and extend the Phase 1/2 results of FCX-007 for the treatment of RDEB wounds and to support a Biologic License Application (BLA) submission in the United States of America (US/USA).

4.2.2. Rationale for Wound Selection, Dose Interval and Dose Selection

Subjects will receive intradermal injections of FCX-007 in each specified treatment wound in two or more treatment sessions. The first treatment session occurs at Day 1 (Visit 2) and the second at Week 12/Month 3 (Visit 3). Additional treatment sessions may occur at Week 24/Month 6 (Visit 4) and Week 36/Month 9 (Visit 5) when unclosed treatment wounds may be re-treated, and unclosed control wounds may be treated. Intradermal injections of FCX-007 0.25 mL per linear cm are administered around the perimeter and across each open wound bed; a maximum of 15 mL may be administered per session.

Wound Selection

Wounds are monitored prior to dosing for at least 12 weeks to characterize eligible persistent non-healing wounds and recurrent wounds. The mechanism of action of FCX-007 supports treatment of persistent non-healing and recurrent wounds (both types of wounds may be chronic). The wound characteristics observed during the monitoring period will be utilized to reduce bias in the pairing of target wounds for treatment and efficacy and safety evaluation.

The wound monitoring period allows remote monitoring of wounds and wound measurements through the image capture of wounds, at least weekly, at bath/RDEB dressing change using the photography vendor's imaging system. Wounds between approximately 5 cm^2 and 50 cm^2 for

subjects 2 to 6 years of age and wounds between approximately 10 cm^2 and 50 cm^2 for subjects 7 years of age and older will be considered as target wounds.

Dose Interval

The clinical progression and healing of individual wounds is not predictable, despite similar underlying biological characteristics. Wounds may heal at variable timepoints after injection, dependent on the size, depth, shape and location of the lesions, affected by continuous or recurrent physical or environmental causes, and systemic and local (epidermal-dermal) biological factors. These or other dynamics may impede wound healing, even in the presence of FCX-007. The Phase 1/2 data supported efficacy at Week 12 following a single administration of FCX-007. At 12 weeks, treated wounds are anticipated to have reduced in size or potentially healed, and repeated dosing at this time may provide the best environment for COL7 expression by FCX-007. A second administration of FCX-007 to each wound 12 weeks after the initial injection (regardless of status of healing), and at 12-week intervals thereafter to wounds that either have not achieved complete closure or that have re-opened after closure is appropriate.

Dose Selection

The concentration of cells administrated at each linear injection point may be an important dosing factor for clinical benefit and COL7 expression. An FCX-007 dose of 1.0 to 3.0 x 10^7 cells/mL, intradermally administered at 0.25 mL per linear cm equates to 2.5 x 10^6 to 7.5 x 10^6 cells/linear cm.

The Phase 1/2 study data support clinical efficacy and COL7 expression within this dose range, and this is corroborated by another clinical study using lentiviral engineered COL7A1-supplemented autologous fibroblasts in adults with RDEB (Lwin, 2018 IID poster; personal communication, Professor John McGrath). In that study, three intradermal injections of 1 x 10^6 cells/cm^2 of modified fibroblasts in intact skin showed a minor increase in COL7 expression and vector was not detected.

The total cell exposure by subject is presented in Table 2. The Phase 1/2 study allowed dosing of up to 4.50 x 10^8 cells per treatment session with four subjects receiving two treatment sessions. Total dose cell exposure ranged from 1.51 x 10^8 to 7.7 x 10^8 cells. A maximum tolerated dose has not been achieved. No detachment of the overlying epithelium was observed by using a 30-gauge needle to inject 0.25 mL of FCX-007 per linear cm along the wound edge or in non-wounded intact skin.

Table 2: Study FI-EB-001 Total Cell Exposure by Subject

Subject Number	Number of Wounds Treated	Treatment Session	Dose (cells/mL)	Cells/ Linear cm	Total Cells Dosed to Wound Sites	Total Cells Dosed to Intact Skin Sites	Total Cell Exposure
101	1	1	2.3×10^7	5.75×10^6	1.21×10^8	3.00×10^7	1.51×10^8
102	2	1	1.4×10^7	3.50×10^6	2.78×10^8	2.10×10^7	2.99×10^8
		2	2.7×10^7	6.75×10^6			
103	2	1	2.5×10^7	6.25×10^6	2.69×10^8	1.50×10^8	4.19×10^8
		2	2.5×10^7	6.25×10^6			
104	2	1	2.0×10^7	5.00×10^6	1.6×10^8	1.33×10^7	1.73×10^8
105	1	1	2.0×10^7	5.00×10^6	4.60×10^8	3.00×10^7	4.90×10^8
		2	2.9×10^7	7.25×10^6			
106	2	1	2.9×10^7	7.25×10^6	7.26×10^8	4.35×10^7	7.7×10^8
		2	2.7×10^7	6.75×10^6			

5. STUDY OBJECTIVES AND ENDPOINTS

The primary efficacy objective is to determine whether administration of FCX-007 in addition to standard of care improves wound healing as compared to standard of care alone (control) in children, adolescents, and adults with RDEB and confirmed mutation of the COL7A1 gene.

Primary efficacy endpoint:

- Complete wound closure of the First Wound Pair at Week 24

Secondary efficacy endpoints:

- Complete wound closure of the First Wound Pair at Week 12
- Complete wound closure of all wounds at Week 24
- Complete wound closure of all wounds at Week 12

Supportive efficacy endpoints:

- Durability of wound closure from Week 24 through Week 48
- Durability of wound closure from Week 24 through Week 36
- Durability of wound closure from Week 12 through Week 48
- Durability of wound closure from Week 12 through Week 36
- Change from baseline in surface area of each wound at Weeks 12, 24, 36, and 48
- Change from baseline in Wong-Baker FACES Pain Rating Scale at Weeks 12, 24, 36, and 48
- COL7 expression in a treated wound as assessed by immunoelectron microscopy (IEM) and immunofluorescence (IF) at Weeks 36 and 48

Safety evaluations include AEs, vital signs, physical and skin examinations, clinical laboratory testing, RCL testing, antibody response to COL7, neoplasms (SCC or sarcoma) and/or inflammation.

6. OVERALL STUDY DESIGN AND PLAN

6.1. GENERAL DESCRIPTION

DEFI-RDEB is a multi-center, intra-patient randomized and controlled, open-label, Phase 3 study of FCX-007 for the treatment of RDEB wounds. FCX-007 is comprised of autologous fibroblasts isolated from the RDEB subject's skin biopsies and transduced with a virus containing the full-length COL7A1 gene to produce functioning type VII collagen.

The Screening Period consists of eligibility criteria evaluations, the collection of one set of three 3-4 mm biopsies for FCX-007 manufacturing, and the identification of and a minimum 12-week Wound Monitoring Period (through photography) of potential target wounds. The subject's potential target wounds will be imaged at the Screening visit by the Investigator or designee, if possible, and subjects will capture wound images via the photography vendor's mobile device-based imaging system at home weekly during this period. The wound characteristics observed during the monitoring period will be utilized to reduce bias in the pairing of target wounds for treatment and efficacy and safety evaluation. The Screening Period is expected to have a duration of approximately 4-6 months, to accommodate subject scheduling and variations in manufacturing duration.

Prior to randomization, target wounds will be identified that meet selection criteria based on review of the photographic images from the Wound Monitoring Period. Up to three target wound pairs, each wound between approximately 5 cm^2 and 50 cm^2 for subjects 2 to 6 years of age and wounds between approximately 10 cm^2 and 50 cm^2 for subjects 7 years of age and older, will be identified for each subject. The Investigator will assign a First (Primary) Pair for primary endpoint evaluation, additional applicable pairs will be designated as Second (Secondary) and Third (Tertiary) Pairs. The First Pair will be the wounds that have been open for the longest duration of time (recorded in weeks, to the closest week) within the Wound Monitoring Period immediately prior to Day 1 (Visit 2), have shown the least variation of wound area over the Wound Monitoring Period and are similar in anatomical location and size. The target wounds in the Second Pair and in the Third Pair will be assigned with similar hierarchical criteria. Following pairing, target wounds will be randomly assigned as the treatment wound (FCX-007 is administered) or control wound.

Subjects will receive intradermal injections of FCX-007 in each specified treatment wound in two or more treatment sessions. Intradermal injections of FCX-007 0.25 mL per linear cm are administered around, and within 1 cm of, the perimeter and across each applicable wound bed; a maximum of 15 mL (in 60 injections) may be administered per session, and the Investigator is encouraged to administer the full quantity of FCX-007 should the total wound size permit. As the wound size and shape will dictate the quantity of FCX-007 to be administered, it is not possible to calculate this until after randomization. As a general rule, the maximum number of injections of FCX-007 is expected to be used over a surface area of approximately 60- 80 cm^2.

The first treatment session occurs at Day 1 (Visit 2) and the second at Week 12/Month 3 (Visit 3). At these visits, the treatment wound in the First Pair will be injected first, followed sequentially by the Second and Third Pairs (if applicable, and only as sufficient product is available). It is permissible for a treatment wound in the Second or Third Pair to be partially

treated due to insufficient quantity of product, if the treatment wound in the First or Second Pair was completely treated.

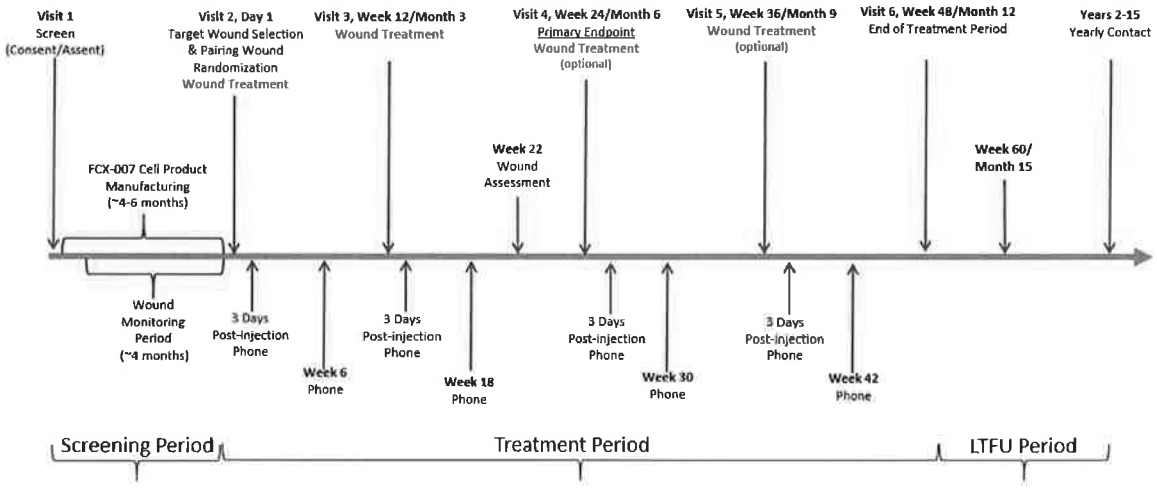
At selected sites only, in a subset of subjects that consent to additional research skin biopsy collection, an additional single treated wound (not from a target wound pair) may be injected with FCX-007 at Day 1 (Visit 2) and Week 12/Month 3 (Visit 3) only.

Additional treatment sessions may occur at Week 24/Month 6 (Visit 4) and Week 36/Month 9 (Visit 5) when unclosed treatment wounds may be re-treated, and unclosed control wounds may be treated.

Safety and efficacy assessments will occur at scheduled intervals through Week 48/Month 12 (Visit 6), when the treatment period is completed, and a long-term safety follow-up period with optional efficacy assessments (through 15 years) commences for subjects who have received one or more FCX-007 injections of any volume.

Refer to Table 3 for the Schedule of Events which provides a summary of study visits, visit windows and assessments and procedures and their associated timings. The study schema is presented in Figure 1.

Figure 1: Study Schema



6.2. STUDY DESIGN RATIONALE

The draft and final Food and Drug Administration (FDA) guidance Gene Therapy for Rare Diseases (FDA, 2018; FDA, 2020) suggests that an intra-patient control approach, such as in rare skin diseases, may be a useful design. Based on our previous experience in the Phase 1/2 study, the suggestion from the guidance and discussions with the FDA, we will continue use of the intra-patient design. Each subject will serve as their own control; subject's target wounds will be paired (target wound pair(s)) then randomized to receive FCX-007 (treatment wound) or remain untreated (control wound). The matched control wounds will be untreated since placebo injections into the matched control wound(s) may cause wound instability, pain, and potentially an economic burden if the wound worsens. Consistent with the FDA's final guidance

Epidermolysis Bullosa: Developing Drugs for Treatment of Cutaneous Manifestations (FDA, 2019), this study was designed to minimize the burden of travel and assessments.

6.3. SAFETY OVERSIGHT

6.3.1. Data Safety Monitoring Board

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

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

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

7. SELECTION OF STUDY POPULATION

. Up to 40 subjects may be screened to ensure a minimum of 24 evaluable subjects for the primary efficacy endpoint.

If applicable, subjects who were treated with FCX-007 in other clinical studies of FCX-007 may be enrolled in the long-term safety follow-up period.

Subjects must meet all of the inclusion criteria and none of the exclusion criteria at Day 1 (Visit 2) prior to wound randomization to be considered eligible for treatment in this study.

Protocol violations from inclusion and exclusion criteria are prohibited because ineligible study subjects can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified is essential.

7.1. INCLUSION CRITERIA

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

1. Subjects and/or their legal guardian must provide written informed consent, in accordance with federal and/or local laws, before any study procedures occur. In addition, if applicable, a minor child must provide written informed assent in accordance with federal and/or local laws as well as in compliance with the recommendations of the approving Institutional Review Board (IRB), before any study procedures occur.
2. Male or female ≥2 years of age at the Screening visit (when consent/assent for study participation is given).
3. Clinical diagnosis of RDEB with confirmation of COL7A1 genetic mutation.
4. At least two eligible persistent non-healing or recurrent wounds identified at Day 1 (Visit 2):
    - Each wound must have an approximate minimum area of 5 cm^2 (subjects 2 to 6 years of age at time of consent) or 10 cm^2 (subjects 7 years of age or older at time of consent) and a maximum of 50 cm^2
    - Wound site was monitored for at least 12 weeks prior to Day 1 (Visit 2) and wound is open (unhealed)
    - The following wounds are excluded:
        - Wounds on a mucous membrane, the face, hands, feet, or fully across joints;
        - Wounds with active infection or evidence of active infection;
        - Wounds that have been previously treated with a gene therapy intervention.
5. Female subjects of childbearing potential and post-pubertal male subjects engaging in sexual activity that could lead to pregnancy who agree to using at least one of the following adequate birth control regimens while in the study and for 6 months after last dose of FCX-007 is administered:
    - Male partner with vasectomy, OR
    - Male condom AND partner use of one of the contraceptive options below:

- Spermicide
- Intrauterine device or intrauterine system
- Oral contraceptive, either combined or progestogen alone
- Contraceptive subdermal implant (e.g., Norplant®)
- Injectable progestogen (e.g., Depo-Provera®)
- Contraceptive vaginal ring (e.g., NuvaRing®)
- Transdermal contraceptive patches (e.g., Ortho Evra®)

- Subjects of childbearing potential who are abstinent are eligible, but they must agree to use one of the birth control regimens listed above if they begin engaging in sexual activity that could lead to pregnancy during the study.
- Periodic abstinence e.g., calendar, ovulation, sympto-thermal, post-ovulation methods and withdrawal are not acceptable methods of contraception.

NOTE: Subjects using an acceptable hormonal based contraceptive must have been on a stable dose for at least 3 months before Day 1 (Visit 2) and be willing to continue stable birth control methods throughout the study.

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

6. Subjects and/or their legal guardian, if applicable, who are, in the opinion of the Investigator, able to understand the study, cooperate with the study procedures and are willing to return to the clinic for all required follow-up visits.

7.2. EXCLUSION CRITERIA

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

1. Female who is pregnant or breastfeeding.
2. Medical instability limiting ability to travel to the investigative site.
3. Active infection with human immunodeficiency virus (HIV), hepatitis B (Hep B) or hepatitis C (Hep C), as determined by Hep B surface antigen screening (HBsAg), detection of HIV or Hep C antibodies, or positive result of Hep C polymerase chain reaction (PCR) analysis.
4. The presence of COL7 antibodies in clinically significant titer by indirect immunofluorescence (IIF) using the subject's serum or COL7 antibodies noted on direct immunofluorescence (DIF) of the subject's skin biopsy.
5. Any clinically significant abnormal laboratory result identified from Day 1 (Visit 2) labs obtained prior to wound randomization.
6. Evidence of systemic infection.
7. Evidence or history of squamous cell carcinoma at the site to be injected.

8. Evidence of or history of metastatic squamous cell carcinoma.
9. Clinically significant abnormalities identified through medical history, AEs and physical examination prior to wound randomization on Day 1 (Visit 2).
10. Known allergy to any of the constituents of the product.
11. Hypersensitivity to anesthesia chosen (lidocaine/prilocaine cream, moderate sedation, or general anesthesia).
12. Active drug or alcohol addiction.
13. Receipt of a systemic or injected chemical or any biological intervention (including gene therapy) for the specific treatment of RDEB within three (3) months prior to initiating the wound monitoring period, or anticipated/planned during the screening and treatment period for this study. (Topical chemical agents *with the exception of biological or gene-therapy* agents may be applied to wounds that are ineligible for inclusion in the study as part of the assigned paired wounds (treated or untreated), (refer to Section 9.9.3).
14. Receipt of chemotherapy (other than topical products for cutaneous pre-cancerous or cancerous lesions) in the past three (3) months prior to screening or anticipated/planned during the screening and treatment period for this study.
15. Receipt of another investigational drug in the past 30 days prior to screening or anticipated/planned during the screening and treatment period for this study.
16. A history of or ongoing serious illness or medical, physical, laboratory abnormality, or psychiatric condition(s) that, in the Investigator's opinion, may interfere with the subject's participation in the study and/or ability to understand and give informed consent.

7.3. PARTICIPATION EXCLUSIVELY IN THE LONG-TERM SAFETY FOLLOW-UP PERIOD

Subjects who have participated in a clinical study with FCX-007 may transfer to this study for the long-term safety follow-up period exclusively. Subjects and/or their legal guardian must provide written informed consent, in accordance with federal and/or local laws, before any study procedures occur. In addition, if applicable, a minor child must provide written informed assent in accordance with federal and/or local laws as well as in compliance with the recommendations of the approving IRB, before any study procedures occur.

7.4. LIFESTYLE RESTRICTIONS

There are no restrictions on skin care however, all target wounds (treatment and control wounds) should receive same standard of care. Routine skin care for RDEB subjects will continue throughout the study.

7.5. SCREEN FAILURES

Screen failures are defined as subjects who consent to participate in the clinical study but do not subsequently undergo wound randomization. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated

Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information will include demography, screen failure details, eligibility criteria, and SAEs, if any.

Subjects who do not meet the criteria for participation in this study (screen failure) because of eligibility criteria will not be rescreened.

Subjects who withdraw prior to FCX-007 administration will be considered a screen failure and will be replaced.

7.6. REMOVAL OF SUBJECTS FROM TREATMENT OR THE STUDY

A subject or their legal guardian is free to discontinue treatment and/or withdraw from the study at any time and for any reason, specified or unspecified, without prejudice to their 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.

Reasons for discontinuation from treatment or the study include, but are not limited to, the following:

- Withdrawal of consent/assent by the subject and/or their legal guardian
    - From the time consent/assent is withdrawn, no additional data should be collected. However, the Sponsor may retain and continue to use data collected before such withdrawal of consent.
- Adverse event
    - It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the subject's discontinuation from treatment or removal from study.
    - A subject may also voluntarily discontinue treatment or withdraw from the study due to what they perceive as an intolerable AE.
- Pregnancy
- Lack of efficacy
- Subject lost to follow-up
- Subject non-compliance
- Investigator or Sponsor decision
- Study terminated by Sponsor
- Other reason

The primary reason for the discontinuation from treatment and/or withdrawal from study must be recorded in the subject's source documents and case report form (CRF). Withdrawal should be discussed with the Medical Monitor prior to withdrawal when possible.

Every reasonable effort should be made to ensure that subjects who have received one or more FCX-007 injections of any volume are retained in the long-term safety follow-up period (through 15 years).

7.6.1. Stopping Criteria

An objective of this study is to generate a safety profile of FCX-007 in subjects with RDEB. Patients with RDEB have a significantly increased risk of experiencing SAEs such as serious infections and SCC relative to the general population; therefore, in most cases, temporary suspension and/or possible discontinuation of the study will be reviewed on a case-by-case basis.

The DSMB may recommend to the Sponsor interruption of FCX-007 administration and/or study enrollment at any time if medically indicated. Occurrence of any of the following observations may trigger a temporary suspension of FCX-007 administration to an individual subject and/or temporary suspension of study enrollment pending a further safety investigation:

1. A treatment-emergent SAE or serious suspected adverse reaction related to FCX-007.
2. Development of an AE suggestive of a retrovirus-associated disease after FCX-007 treatment. Attempts will be made to collect any relevant clinical samples for available RCL testing.
3. A positive RCL qPCR assay result. A positive RCL qPCR assay will result in suspension of FCX-007 administration. The result should be confirmed by conducting a biological-based (culture-based) assay.
4. Any systemic infection designated as suspected to be related to FCX-007 or contamination during the administration of FCX-007.
5. A treatment-emergent uncontrolled bacterial, viral, or fungal infection in a wound that was administered IP where product sterility testing results reported post-injection were positive for contamination.
6. For any subject who dies or is diagnosed with a neoplasm after FCX-007 treatment, attempts will be made to collect a biopsy of the neoplastic tissue or pertinent autopsy tissue to assay for available RCL testing by qPCR. A positive RCL result will cause product administration to be suspended.

For subject safety, Investigators should continue to follow subjects in accordance with study visits and procedures as outlined in the protocol. An occurrence of any of these safety observations will be shared with all study Investigators, the DSMB and the appropriate regulatory authorities. The DSMB will review the results of the safety investigation and may request any additional data needed to assess the safety of restarting study dosing and/or study enrollment. The DSMB will recommend to the Sponsor if the suspension can be lifted (with or without amending the protocol) or if the trial will need to terminate based on their review of the safety investigation.

7.6.2. Withdrawal Procedures

Discontinuation of FCX-007 administration does not mean discontinuation from the study. The study assessments and other procedures for the visit and subsequent visits should be completed as indicated in the Schedule of Events (Table 3), and reason for discontinuation of FCX-007 administration should be documented in the subject's source documents and CRF.

If a subject discontinues prior to commencing the long-term safety follow-up period, every effort must be made to perform the study assessments and procedures specified for Visit 6, End of

Treatment (EOT), within 12 weeks (Section 8.5.2.4). The primary reason for subject's withdrawal should be documented in the subject's source documents and CRF.

Every reasonable effort should be made to ensure that subjects who have received one or more FCX-007 injections of any volume are retained in the long-term safety follow-up period (through 15 years).

7.6.3. Lost to Follow-Up

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.

A subject will be considered lost to follow-up if they fail to return to the investigative site for scheduled visits and is unable to be contacted by the investigative site staff.

Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject and/or their legal guardian.

- The Investigator or designee must attempt to reach the subject and/or their legal guardian twice by telephone and once by certified letter using the subject's last known mailing address. These contact attempts should be appropriately documented, and a copy of the follow-up letter maintained in the subject's source documents.
- Should the subject continue to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up. The end of participation for a subject lost to follow-up is documented as the date of, or receipt of (if applicable), the certified letter.

7.6.4. Sponsor Study Suspension or Termination

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB, drug safety problems, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of the referenced investigational drug at any time.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Investigator's insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

If the study is prematurely terminated or discontinued, the Sponsor or its designee will promptly notify the Investigator. After notification, the Investigator or designee must promptly inform all

participating study subjects, notify the IRB in writing of the early termination and send a copy of the notification to the Sponsor or its designee.

As directed by the Sponsor, all study materials must be collected and all CRFs completed to the greatest extent possible.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. SCHEDULE OF STUDY VISITS AND ASSESSMENTS

Study visit schedule, visit windows and assessments and procedures and their associated timings are summarized in the Schedule of Events (Table 3). Every effort should be made to adhere to the study assessments and procedures, visit schedule and visit windows as specified in the Schedule of Events. Visit windows for in-clinic visits and phone contacts (PC) are calculated in relation to Day 1 (Visit 2), with the exception of PCs 3 days post-injection (which each correspond to the most recent injection date), and the Week 22 wound assessment (WA) contact (which is relative to the anticipated Week 24 visit).

Additional information about the specific assessments and procedures can be found in Sections 8.2, 8.3, and 8.4.

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

Table 3: Schedule of Events

		V1	V2	PC1/PC2	V3	PC3/PC4	WA	V4	PC5/PC6	V5	PC7/PC8	V6 (EOT)
		Screening/ Wound Monitoring[1]	Day 1	3 Days Post-injection[2] & Week 6	Week 12 (Month 3)	3 Days Post-injection[2] & Week 18	Week 22	Week 24 (Month 6)	3 Days Post-injection[2] & Week 30	Week 36 (Month 9)	3 Days Post-injection[2] & Week 42	Week 48 (Month 12; Year 1)
				-1/+3 days / -/+1 week	-1/+4 weeks	-1/+3 days / -/+1 week	-21 to -11 days prior to Week 24*	-1 /+4 weeks	-1/+3 days / -/+1 week	-1/+4 weeks	-1/+3 days / -/+1 week	-1 /+4 weeks
	Informed Consent / Assent / HIPAA	X										
	Inclusion / Exclusion Criteria	X	X									
	Demographics, Medical/Surgical History	X										
	Physical Exam[20]	X	X					X				X
	Skin Exam[20]	X	X		X			X		X		X
	Vital Signs	X[3]	X[3]		X			X		X		X[3]
	Prior/Concomitant Medications including Skin/Wound Care Regimen	X	X	X	X	X		X	X	X	X	X
	Adverse Events[4]	X	X	X	X	X		X	X	X	X	X
Wound Assessment	Potential Target Wounds Identification / Mapping	X										
Wound Assessment	Digital Imaging / Wound Measurements[5]	X	X		X			X		X		X
Wound Assessment	Target Wounds Selection/Mapping/Pairing/ Tracing (optional)/Labeling/Randomization[21]		X									
Wound Assessment	Investigator Assessment of Complete Wound Closure of Target Wounds[20]				X[17]		X[17,18]	X[17]		X		X
Wound Assessment	Wong-Baker FACES® Pain Assessment		X		X			X		X		X
	FCX-007 Administration[6]		X		X			X[19]		X[19]		
Blood, Urine & Culture Tests	*Local Laboratory Testing:*											
Blood, Urine & Culture Tests	Bacterial Wound Culture, if applicable[7]		X		X			X		X		X
Blood, Urine & Culture Tests	Urine Pregnancy Test, if applicable[8]	X	X		X			X		X		X
Blood, Urine & Culture Tests	HIV, Hep B, & Hep C	X										
Blood, Urine & Culture Tests	Hematology & Chemistry[20]	X	X[16]		X			X		X		X
Blood, Urine & Culture Tests	*Outside Laboratory Testing:*											
Blood, Urine & Culture Tests	Genetic Testing[9]	X										
Blood, Urine & Culture Tests	RCL Analysis[20]	X[10]			X			X		X		X
Blood, Urine & Culture Tests	COL7 Antibody Assay[20]	X[10]			X			X		X		X
	(3) 3-4 mm biopsies/FCX-007 manufacturing[11]	X										
	(1) biopsy for DIF (COL7 antibodies)	X[12]			X[13]			X[13]		X[13]		X[13]
	Biopsy for H&E, if applicable[14]				X			X		X		X
	Optional Biopsy: (1) biopsy for IF (COL7 expression), if applicable[15]	X						X		X		X
	Optional Biopsy: (1) biopsy for IEM, if applicable[15]	X						X		X		X

V=Visit, PC=Phone Call, WA=Wound Assessment, EOT= End of Treatment. An unscheduled visit, with necessary assessments, may occur as needed.

*** Week 22 visit window is relative to scheduled Week 24 visit day (all others relative to Day 1, except the PCs 3 days post-injection which each correspond to the most recent injection date).**

1. Screening visit may occur over multiple visits, however, informed consent must be performed at the first screening visit and collection of biopsies for FCX-007 manufacturing (if not previously obtained) should also be performed at the first screening visit, or as soon as possible thereafter. The Screening Period includes the identification/mapping/selection/labeling and imaging of potential target wounds that are followed minimally for a 12-week period Wound Monitoring Period.
2. Phone call to subject if FCX-007 was administered at prior visit (not required if FCX-007 was not administered).
3. Height and weight will be measured at Screening, Day 1 (V2), and Week 48/Month 12 (V6). At Day 1 and Week 48, height and weight may be collected within 1 day prior to the visit.
4. For any subject who develops an adverse event suggestive of a retrovirus-associated disease after FCX-007 treatment, attempts will be made to collect any relevant clinical samples for available RCL testing. For any subject who dies or is diagnosed with a neoplasm after FCX-007 treatment, attempts will be made to collect a biopsy of the neoplastic tissue or pertinent autopsy tissue to assay for available RCL testing.
5. Mobile device and associated supplies for wound imaging will be provided to subject (or caregiver) and investigative site personnel will provide instructions for use at Screening. Subject (or caregiver) will capture wound images via the photography vendor's mobile device-based imaging system at home at least weekly at a minimum, 12 weeks prior to Day 1 through Week 24 (Visit 4) at bath/RDEB dressing changes (preferably after bathing), thereafter weekly imaging is optional. Investigator or designee will capture wound images at clinic visits; may be completed within 1 day prior to the visit (V2-6). Mobile device for wound imaging will be collected from subject at Week 48 visit.
6. Administration of FCX-007 will not occur in a specific treated wound if: 1) the treated wound shows unusual inflammation (beyond temporary inflammation 1-2 days post-injection) suspected to be related to the investigational product (IP), based upon the Investigator's judgment; or 2) an area injected with IP shows unusual growth.
7. To be performed as needed, based upon standard of care and Investigator's judgment, if clinical evaluation is indicative of infection. May be completed within 1 day prior to the visit.
8. Required for all female subjects of childbearing potential; urine pregnancy testing must be performed prior to FCX-007 administration. If positive pregnancy test, FCX-007 will not be administered. May be completed within 1 day prior to the visit.
9. A blood sample for genetic testing is not required if RDEB genetic diagnosis has been confirmed and results are contained in the subject's medical records.
10. RCL analysis and/or COL7 antibody assay are not required to be drawn at Screening if performed within the prior 2 years and results are contained in the subject's medical records.
11. Skin biopsies for FCX-007 manufacturing do not need to be collected if previously obtained in prior clinical study (i.e., FI-EB-001). An additional set of skin biopsies may be collected if the manufacturing process does not yield an FCX-007 cell count sufficient for one FCX-007 treatment session or do not meet release specifications.
12. A skin biopsy for DIF is required at Screening if: 1) subject did not previously have a skin biopsy for DIF performed and results are not contained in the subject's medical records; or 2) the subject was enrolled in a gene therapy trial for EB and did not have a skin biopsy for DIF performed following participation and results are not contained in the subject's medical records.
13. A skin biopsy for DIF is required if: 1) treated wound shows unusual inflammation (beyond temporary inflammation 1-2 days post-injection) suspected to be related to the IP, based on Investigator's judgement; or 2) a post-treatment COL7 serum antibody assay is newly positive or has a clinically significant increased titer from Screening. An unscheduled earlier visit may occur as needed.
14. A skin biopsy for hematoxylin and eosin (H&E) may be collected if: 1) an area injected with IP shows unusual growth; or 2) a DIF biopsy is being collected post-treatment and the investigator feels that the H&E biopsy will add additional information to the DIF biopsy.
15. Optional skin biopsies for IF and IEM will be collected in a subset of subjects that consent to additional biopsies. Baseline biopsies may be collected at any time prior to FCX-007 Day 1 injections and are not required if previously performed and results are contained in the subject's medical records. Biopsies at later intervals are only to be performed if there is a baseline (or prior) biopsy for same evaluations, and biopsies at Weeks 36/Month 9 (V5) and 48/Month 12 (V6) need only be obtained if the prior biopsy demonstrated COL7 expression (for IF) and/or relevant structural changes (for IEM).
16. Results must be reviewed prior to final eligibility determination on Day 1 (V2), the labs may be performed on day of visit, or within 7 days prior to this visit.
17. Blinded assessment is required at Week 12/Month 3 (V3), Week 22, and Week 24/Month 6 (V4 may be completed within 1 day prior to the visit if this is still within the Week 24 Visit window and does not interfere with the time from the Week 22 assessment).
18. Wound assessment (WA) at Week 22 may be performed via remote video assessment, assessment of adequate and current wound imaging, or during a clinic visit.
19. At Week 24/Month 6 (V4) and Week 36/Month 9 (V5) unclosed treatment wounds may be re-treated and unclosed control wounds may be injected.
20. May be completed within 1 day prior to the visit unless otherwise noted.
21. Target wound selection, mapping, pairing, tracing, and labeling may be completed within 1 day prior to the visit. Randomization **must** take place on the day of the visit.

LONG-TERM FOLLOW-UP		
	Week 60 (Month 15) [1]	**Years 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 (Months 24 | 36 | 48 | 60 |72 | 84| 96 | 108 | 120 | 132| 144 | 156 | 168 | 180)**
	±4 weeks	**±8 weeks**
Contact subject to review/record the following, ideally scheduled to follow annual visits and assessments (including relevant laboratory analyses) performed by the subject's health care provider: • Concomitant Medications/Exposure to Mutagenic Agents and Other Medicinal Products • Adverse Events of Special Interest / Emergence of New Clinical Conditions, including, but not limited to: o New malignancy(ies) o New incidence or exacerbation of a pre-existing neurologic disorder o New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder o New incidence of a hematologic disorder o Unexpected illnesses and hospitalization(s)		X
Investigator Assessment of Complete Wound Closure (optional, does not apply to subjects who were treated in study FI-EB-001)	X[6]	X[6]
Laboratory Testing		
Blood for RCL Analysis[2]	X	X
Biopsy of Neoplastic Tissue or Pertinent Autopsy Tissue Collection for RCL Analysis[3]		X
Skin Biopsy for Off-target Activity (Insertional Mutagenesis) Testing[4]		X
Optional Biopsy: Skin Biopsy for Transgene and Vector Persistence[5]		X

1. Not required for subjects that only received IP administration on Day 1 in study FI-EB-002, or those who enroll only into the long-term follow-up portion of the study.
2. Collection and analysis of a blood sample to monitor for RCL may be performed yearly for up to 15 years. If all post-treatment RCL assays are negative through one year following subject's final IP administration (Week 60 for those who received last injection of FCX-007 at Week 12, or Year 2 for those who received last injection at Week 24 or 36), collection of the yearly follow-up samples may be discontinued.
3. For any subject who is diagnosed with or dies of a new malignancy, attempts will be made to collect a biopsy of the neoplastic tissue or pertinent autopsy tissue to perform relevant RCL testing.
4. For any subject with a malignant growth in a region of FCX investigational gene therapy administration, attempts will be made to collect a skin biopsy of the malignant tissue for viral vector presence and potentially clonality of vector integration testing, as available.

5. In years 2-6 only (or 1-5 years after the final administration of IP), a skin biopsy from the region of FCX investigational gene therapy administration (i.e., treated skin area) may be taken to test for relevant transgene and vector persistence *in subjects who consent to the collection of the biopsies required to perform the assay*. However, collection of biopsies will stop if transgene and vector persistence is undetected.
6. Only applies if the treatment wound was closed at Week 48 (Month12/Year 1) and is no longer assessed if the treatment wound reopens. Wound assessment should be performed via remote video assessment.

8.2. BASELINE CHARACTERISTICS

8.2.1. Demographics

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

8.2.2. Medical/Surgical History / Prior and Concomitant Medications

Medical/surgical history will be collected at the Screening visit to ensure subjects are eligible for participation in the study (per inclusion Section 7.1 and exclusion Section 7.2 criteria).

The Investigator or designee will collect a complete medical history at the Screening visit, including review of subject's prior and concomitant medications (per Section 9.9). The medical history will include review and recording of dermatological (including RDEB history, history of SCC and any recent skin infections), neurological, ophthalmic (including review of keratitis), ear/nose/throat, cardiovascular, respiratory, gastrointestinal (including review of nutritional deficiencies, anorexia, dysphagia, failure to thrive, need for gastrostomy, constipation, esophageal dilation history, oral pain, and dental issues), hematologic (including history of anemia, hypoalbuminemia, previous treatments including transfusions and iron supplementation), endocrine, renal, hepatic, psychiatric and other conditions/diseases (such as history of bone pain), as well as allergies (drug, food, environmental).

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

8.2.3. Skin Biopsy for FCX-007 Manufacturing

Three (3) 3-4 mm skin biopsies for the purpose of FCX-007 manufacturing will be collected at the first Screening visit if not previously obtained in a prior FCX-007 study (i.e., FI-EB-001). Biopsies will be collected from subject's normal/unaffected/intact skin with the specific location varying on a case-by-case basis based on the Investigator's judgment (refer to Appendix 1 for additional collection site guidance).

An additional set of skin biopsies may be collected if the manufacturing process does not yield an FCX-007 cell count sufficient for at least one treatment session or does not meet release specifications.

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

8.3. EFFICACY ASSESSMENTS

8.3.1. Wound Assessments by Unblinded and Blinded Investigators

Screening and Baseline assessments necessary for identification, mapping, selection, and labeling of wounds are to be performed by the PI, or trained, medically qualified Sub-I, who will remain unblinded to wound treatment assignment throughout the study.

The Investigator Assessment of Complete Wound Closure of Target Wounds must be performed by a Blinded Investigator at at Weeks 12, 22, and 24 (Table 3). Blinded assessment is also preferred at Weeks 36 and 48.

At all Long-Term Follow-Up visits, the Investigator Assessment of Complete Wound Closure by remote video assessment is encouraged but optional for **treated** Target Wounds (treatment wound), the wounds originally designated as control should not be assessed. This assessment should occur only if the treated Target Wound was closed at Week 48 (Month 12/Year 1) and should cease at further visits if the treated Target Wound is open at any Long-Term Follow-Up visit.

This assessment is to be completed after removal of subject's dressings from target wound pairs (treatment and control wounds) **and prior to any potential disruption of the target wounds** (i.e., surgical pen markings, target wound tracing, bacterial culture of wounds if applicable, FCX-007 administration preparation or administration, or collection of biopsies).

The Blinded Investigator will not have access to the subject's source documents, CRFs, or electronic data capture (EDC) as information regarding target wound randomization and treatment information is available. The Blinded Investigator's assessments will be maintained as separate source documents and stored in a separate location. Written or verbal communication about treatment assignment or interval changes in wounds between those involved in administering FCX-007 (including study team members, subjects and those accompanying subjects at any visit, or others who have knowledge of the wound treatment assignment) and the Blinded Investigator will be discouraged, and a verbal reminder of this requirement will be stated by the Blinded Investigator at the time of the assessments.

8.3.1.1. Potential Target Wound Identification, Mapping, Selection and Labeling

Potential target wound identification, mapping, selection, and labeling will be performed at the Screening visit as indicated in the Schedule of Events (Table 3).

A preliminary evaluation of potential target wounds will occur at the Screening Visit. Potential wounds that meet criteria (specified below) will be identified, mapped, and labeled at Screening. **A minimum of 4 wounds should be identified if possible, to ensure the presence of at least 2 eligible wounds.** The duration of time since the wound was identified should be recorded. Additional wounds may also be identified during the Wound Monitoring Period. Upon coordination with the PI/site, these wounds may be included as potential target wounds and must have a minimum 12-week monitoring prior to dosing.

Criteria for Potential Target Wounds:

- Persistent non-healing or recurrent wounds, as per report of subject or guardian or clinical notes.
- Approximate minimum area of 5 cm^2 (subjects 2 to 6 years of age) or 10 cm^2 (subjects 7 years of age and older) and a maximum of 50 cm^2.
- The following wounds are excluded:
    - Wounds located on a mucous membrane, the face, hands, feet, or fully across joints.
    - Wounds that have been previously treated with a gene therapy.

Potential target wounds will be labeled by a continuous sequential number, i.e., Potential Wound 01 (P01) through Pnn.

8.3.1.2. Target Wound Selection, Mapping, Pairing and Labeling

At Day 1 (Visit 2) following the skin examination, the Investigator will select, map (i.e., location recorded by anatomic location and specific location), pair (per hierarchical criteria below) and label target wounds that meet selection criteria (specified below) based on imaging results from the Wound Monitoring Period. Depending on the size of the largest wound in the target wound pair and number of total wounds identified in the monitoring period, up to three pairs of target wounds may be identified for each subject.

Selection Criteria for Final Target Wounds:

1. Must have an approximate minimum area of 5 cm^2 (subjects 2 to 6 years of age) or 10 cm^2 (subjects 7 years of age and older) and maximum area of 50 cm^2,
2. Monitored for at least 12 weeks before Day 1 (Visit 2), and wound is open (unhealed),
3. Wounds were individually isolated and did not become confluent during the Wound Monitoring Period,
4. Wounds should appear clean with adequate granulation tissue, vascularization, and not appear infected.
5. The following wounds are excluded:
    - Wounds on a mucous membrane, the face, hands, feet, or fully across joints,
    - Wounds with active infection or evidence of active infection,
    - Wounds that have been previously treated with a gene therapy intervention.

Pairing and Labeling of Final Target Wounds:

Following selection of final target wounds, the Investigator will pair the target wounds (target wound pair(s)) according to the following hierarchical criteria, and then assign the target wound pair(s) as First (Primary), Second (Secondary), and Third (Tertiary) Wound Pair(s), as applicable. The criteria to assess, in order of importance, for wounds to include in the Target Wound Pairs follow.

1. Duration of time (recorded in weeks, to the closest week) within the Wound Monitoring Period that the wound has been open immediately prior to Day 1 (Visit 2),
2. Variability of change in surface area, based on investigator's review of images in the photography vendor's imaging system, throughout the Wound Monitoring Period,
3. Size, and
4. Anatomical location.

Based on the criteria above, the wounds in the **First Wound Pair** will be wounds that:

1. Have been open for the longest duration of time immediately prior to Day 1 (Visit 2),
2. Have shown the least variability of change in surface area,
3. Are similar in size, and
4. Are similar in anatomical location.

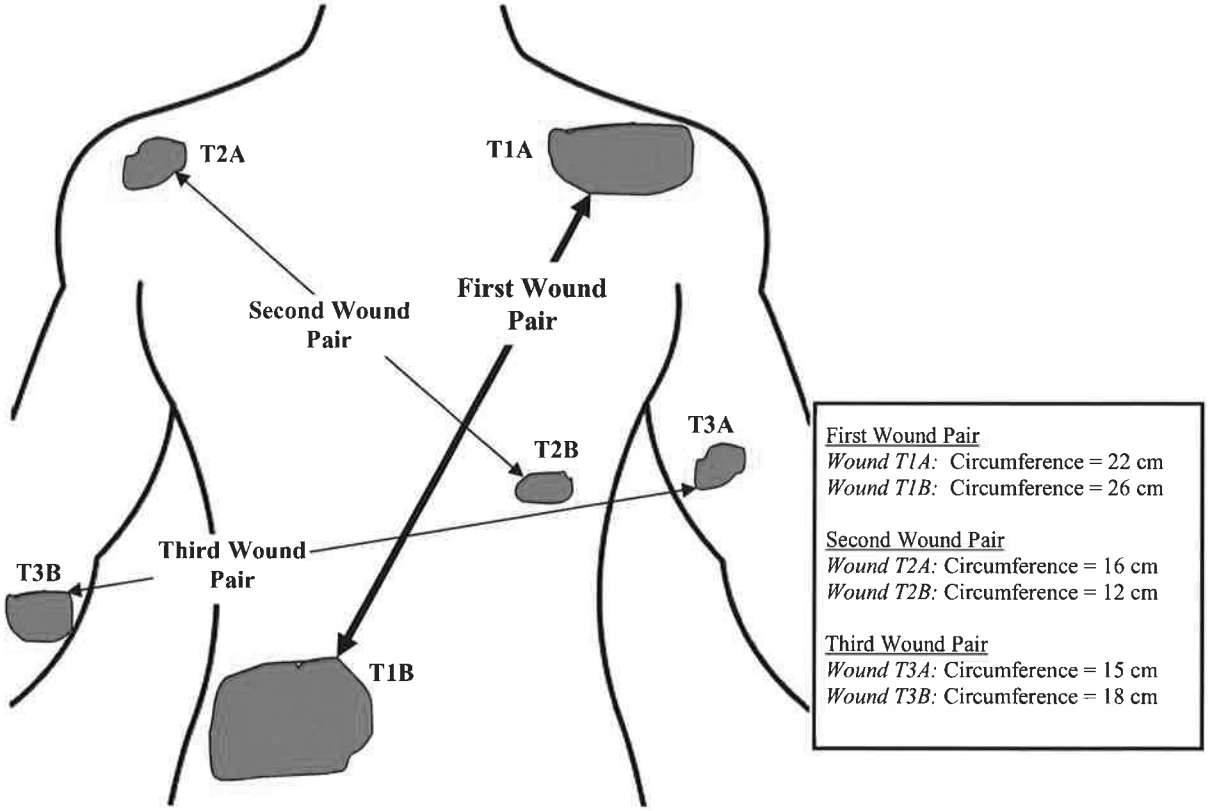
The target wounds in the Second Wound Pair may have been open for a shorter duration, have more variability of change in the surface area and wider variation in size and anatomical location, and the wounds in the Third Wound Pair following a similar pattern of criteria.

The final selected target wound pair(s) will be ordered and labeled as follows:

1. T1A and T1B for the First Wound Pair,
    - The wound labeled as the "A" wound in each target wound pair should be superior (cephalic) in body location to the other wound in the pair which would be labeled the "B" wound. If both wounds are on the same horizontal plane, then the target wound on or toward the subject's left-side of the body would be labeled as the "A" wound and the other wound would be labeled the "B" wound.
2. T2A and T2B for the Second Wound Pair, and
3. T3A and T3B for the Third Wound Pair.

Figure 2 provides an example of pairing and labeling wounds for a subject in which three target wound pairs are selected for inclusion in the study, and assumes the First Wound Pair has been open for the longest duration of time immediately prior to Day 1 (Visit 2), and the Third Wound Pair for the shortest time period. The First Wound Pair should be selected with the intent to fully treat the entire wound.

Figure 2: Wound Pairing, Labeling and Selection Example: Size and Location Criteria



Selection and Labeling of (Optional) Biopsy Wounds:

At selected sites only, in a subset of subjects that consent to additional research skin biopsy collection, an additional single treated wound (not from a target wound pair) may be injected with FCX-007 at Day 1 (Visit 2) and Week 12/Month 3 (Visit 3) only. This may be identified as wound BXL.

8.3.1.3. Assessment of Complete Wound Closure of Target Wounds

Investigator Assessment of Complete Wound Closure of Target Wounds must be performed by a Blinded Investigator at Weeks 12, 22, and 24 (Table 3). Blinded assessment is also preferred at Weeks 36 and 48. The assessment is to be completed after removal of subject's dressings from target wound pairs (treatment and control wounds) **and prior to any potential disruption of the target wounds** (i.e., surgical pen markings, target wound tracing, bacterial culture of wounds if applicable, FCX-007 administration preparation or administration, or collection of biopsies).

Complete Wound Closure is defined as skin re-epithelialization without drainage. Dried serous or hemorrhagic crust or other debris may be present on epithelialized wound surfaces and may include debris from adjacent wounds or dressings. Removal of the debris from the treated or control wound may cause trauma to the wound and cause removal of intact epithelium. The subject may utilize standard-of-care wound dressings and/or garments intended to protect the

wound and adjacent areas from lateral friction, and the use of such dressings does not necessarily suggest an absence of epithelium.

8.3.1.4. Target Wound Tracing

Target wound tracing using flexible transparencies should be performed at Day 1 (Visit 2) after the Wong-Baker FACES Pain Assessment and capturing the digital image of target wounds at the visit are performed and prior to FCX-007 administration and collection of biopsies. Please note: target wound tracing must be performed if tattooing around target wounds is not performed.

Target wound tracings on a flexible transparency will be used to aid in the identification and assessment of the target wound margins/edges as necessary (e.g., target wounds with blurred outlines or adjacent to another wound). Wound tracing is strongly urged in order to enable: 1) the blinded assessor in confirming the original perimeter/area of the wound when performing the Investigator Assessment of Complete Wound Closure of Target Wounds, and 2) the investigator in determining where subsequent injections should be administered if wound healing occurs (refer to Protocol Section 9.7 for additional details).

8.3.2. Digital Imaging / Wound Measurement

Digital imaging and wound measurements will be captured at the time points indicated in the Schedule of Events (Table 3) using the photography vendor's mobile device-based imaging system.

The photography vendor's imaging system offers a comprehensive set of viewing and measurement tools. The photography vendor's system will capture and provide wound measurement information such as calculation of wound length, width, perimeter, and surface area as well as change in each measurement. To ensure compliance with the cataloging and tracking of all images, each image will be timestamped using Part 11 compliant software.

Images will be oriented and captured in follow-up visits for the purpose of assessing wound healing progress. Wound areas will be traced using the software and compared to baseline area measurements to calculate wound closure at each visit.

Screening Visit:

At the Screening visit, following identification, mapping, selection, and labeling of potential target wounds (refer to Section 8.3.1.1 for details), the Investigator or designee will take images of each potential target wound if possible, otherwise the subject will take the initial image of the potential target wound at home. In addition, the investigative site personnel will provide the mobile device and associated supplies for wound imaging to the subject or their caregiver and provide instructions for use.

Wound Monitoring Period:

During the Wound Monitoring Period, the subject or their caregiver will capture images of the potential target wounds at home at least weekly at bath/RDEB dressing change (preferably images will be taken after bathing). Additional wounds may also be identified and imaged during the Wound Monitoring Period. Upon coordination with the PI/site, these wounds may be

included as potential target wounds and must have minimum 12-week monitoring prior to dosing. The images will be viewed and followed by the Investigator.

If the subject returns to the clinic during the Wound Monitoring Period, the Investigator or designee may image the subject's wounds.

Treatment Period

During the Treatment Period, the subject or their caregiver will capture images of the target wounds (treated and control) at home at least weekly through Week 24 (Visit 4), with weekly imaging optional thereafter, at bath/RDEB dressing change (preferably images will be taken after bathing) and the Investigator or designee will capture images of the target wounds (treatment and control) at visits specified.

During visits, images of target wounds (both treatment and control) will be taken prior to any potential disruption of the target wounds (i.e., surgical pen markings, target wound tracing, bacterial culture of wounds if applicable, FCX-007 administration, or collection of biopsies).

* Images of target wounds (both treatment and control) taken by site personnel at Day 1/Visit 2, Week 12/Visit 3, Week 24/Visit 4, Week 36/Visit 5, and Week 48/Visit 6 **must** be reviewed to ensure the accuracy of the photography vendor's automated tracing of wound boundaries. If TA's automated tracing is not accurate, the wound boundaries must be retraced manually.

Day 1 (Visit 2):

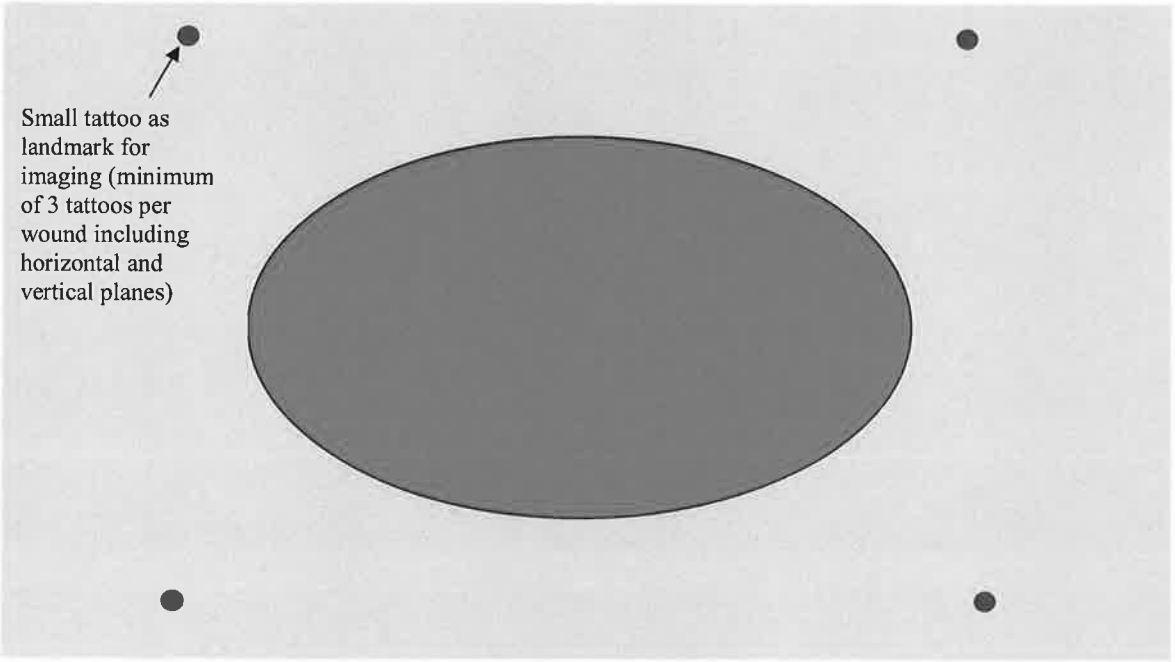
1) Following target wound selection, mapping, pairing, and labeling (refer to Section 8.3.1.2 for details) at Day 1 (Visit 2), small tattoos may be placed on non-blistered skin near target wounds (both treatment and control) as a landmark for imaging and to aid in the assessment of the target wound margins/edges as necessary (refer to Figure 3).
2) Images (baseline images) of the target wounds (both treatment and control) at the visit will be taken by the Investigator or designee after tattooing as applicable and before surgical pen marks are made.
3) Following tattooing as applicable, and imaging, surgical pen marks will be made to indicate the injection sites for each treatment wound (refer to Section 9.7.1 for additional details).

Week 12/Month 3 (Visit 3), Week 24/Month 6 (Visit 4), Week 36/Month 9 (Visit 5), and Week 48/Month 12 (Visit 6):

1) If previously placed tattoos faded, small tattoos may be placed again at sites previously tattooed at Day 1 (Visit 2) on non-blistered skin near the target wounds (both treatment and control) (refer to Figure 3). (This step is not required at Week 48/Month 12.)
2) Images of the target wounds (both treatment and control) at the visit will be taken by the Investigator or designee after tattooing as applicable and before surgical pen marks are made (if applicable).

Details of the clinical photography procedures will be contained in the Study Procedures Manual.

Figure 3: Target Wound Markings – Tattoos



8.3.3. Wong-Baker FACES® Pain Assessment

The Wong-Baker FACES Pain Rating Scale was originally created for children to communicate about the level of their physical pain, but is now used with people ages 3 and older. The Wong-Baker FACES Pain Rating Scale will be administered to all subjects ages 3 years and older on Day 1 (Visit 2), at the time points indicated in the Schedule of Events (Table 3) **prior to any potential disruption of the target wounds** (i.e., surgical pen markings, target wound tracing, bacterial culture of wounds if applicable, FCX-007 administration preparation or administration, or collection of biopsies). While the scale is designed and validated for general physical pain, each subject will be instructed in the use of the scale and will select a face that illustrated the pain they are experiencing in each identified treatment and control wound.

The Wong-Baker FACES Pain Rating Scale is provided in Appendix 2.

8.3.4. Optional Research Biopsies

At selected sites only, in a subset of subjects that consent to additional skin biopsy collection, research biopsies for IF and IEM analysis from an additional single treated wound (not from a target wound pair) may be collected at the time points indicated in the Schedule of Events (Table 3). This wound will only be treated at Day 1 (Visit 2) and Week 12/Month 3 (Visit 3).

Baseline biopsies may be collected at any time prior to FCX-007 Day 1 injections. Baseline biopsies for IF and IEM are not required if previously performed and results are contained in the subject's medical records. Biopsies at Weeks 36/Month 9 (Visit 5) and 48/Month 12 (Visit 6) need only be obtained if the prior biopsy demonstrated meaningful change from baseline (that is, demonstrated COL7 expression or structural changes).

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

8.3.4.1. Skin Biopsy for Immunofluorescence

At selected sites only, in a subset of subjects that consent to additional skin biopsy collection, a skin biopsy for IF will be collected at the time points indicated, as applicable. The following will be reported:

- COL7 expression

* A baseline biopsy will be collected from the subject's normal/unaffected/intact skin (refer to Appendix 1 for additional collection site guidance). Collection of a baseline skin biopsy for IF is not required if previously performed and results are contained in the subject's medical records.

A biopsy at Weeks 36/Month 9 (Visit 5) and 48/Month 12 (Visit 6) need only be obtained if the prior biopsy demonstrated COL7 expression. The biopsy will be collected from the single treated wound (not from a target wound pair) from intact/healed skin at or very close to the site of IP administration.

Biopsy analysis for IF will occur at an outside lab.

8.3.4.2. Skin Biopsy for Immunoelectron Microscopy

At selected sites only, in a subset of subjects that consent to additional skin biopsy collection, a skin biopsy for IEM will be collected at the time points indicated, as applicable.

* A baseline biopsy will be collected from the subject's normal/unaffected/intact skin (refer to Appendix 1 for additional collection site guidance). Collection of a baseline skin biopsy for IEM is not required if previously performed and results are contained in the subject's medical records.

A biopsy at Weeks 36/Month 9 (Visit 5) and 48/Month 12 (Visit 6) need only be obtained if the prior biopsy demonstrated relevant structural changes. The biopsy will be collected from the single treated wound (not from a target wound pair) from intact/healed skin at or very close to the site of IP administration.

Biopsy analysis for IEM will occur at an outside lab.

8.4. SAFETY ASSESSMENTS

The Investigator must access and promptly review the results of all safety assessments including physical and skin examinations, vital signs, laboratory testing, and AEs throughout the study.

8.4.1. Physical Examination

Physical examinations will be performed at the time points indicated in the Schedule of Events (Table 3).

The PI or medically qualified Sub-I will perform the physical examination; body systems evaluated will include:

- General appearance
- Head, Ears, Eyes, Nose, Throat
- Spine/Neck/Thyroid
- Respiratory
- Cardiovascular
- Abdomen
- Nervous System
- Musculoskeletal

Abnormalities noted during the physical examination should be reported in the source document. Any clinically significant physical examination finding(s), based upon the opinion of the Investigator, identified during the Screening examination will be recorded as medical history.

8.4.2. Skin Examination

Skin examinations will be performed at the time points indicated in the Schedule of Events (Table 3).

The PI or medically qualified Sub-I will perform the skin examination of wounds at Screening, and on the wounds in the First, Second and Third wound pairs at all Treatment Period visits as applicable.

- If a treated wound shows unusual inflammation (beyond temporary inflammation 1-2 days post-injection) suspected to be related to IP, based upon the Investigator's judgment, a skin biopsy for DIF will be collected (refer to Section 8.4.4.8 for additional details).
- If the area injected with IP shows unusual growth or inflammation, a skin biopsy for H&E will be collected (refer to Section 8.4.4.9 for additional details).

Abnormalities noted during the skin examination should be reported in the source document. Any clinically significant skin examination finding(s), based upon the opinion of the Investigator, identified during the Screening examination will be recorded as medical history.

8.4.3. Vital Signs

Vital signs will be measured at the time points indicated in the Schedule of Events (Table 3).

Vital signs will be measured before removing RDEB dressings and blood or biopsy collection and will include measurement of height and weight (at Screening and Day 1 (Visit 2), and Week 48/Month 12 (Visit 6) only), systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature. Subjects should be in a seated position for at least 5 minutes before measurement of systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature. Blood pressure determined by cuff (manual or automated) is acceptable although the same method should be used throughout the study. Temperature determined by oral, tympanic or temporal thermometer, is acceptable although the same method should be used throughout the study.

Any clinically significant vital sign measurement, based upon the opinion of the Investigator, identified at the Screening visit will be recorded as medical history

8.4.4. Laboratory Assessments

All protocol-required laboratory assessments will be performed at the time points indicated in the Schedule of Events (Table 3). Whenever possible, the amount of blood collected should be minimized.

Reference ranges for all local laboratory assessments will be supplied by the laboratory and collected by the Sponsor or its designee to use to assess the laboratory data for clinical significance and out-of-range pathological changes.

Clinical laboratory data (i.e., hematology, chemistry, bacterial culture) will be evaluated by the PI or medically qualified Sub-I and clinical significance will be assessed for abnormal values and the assessment will be documented on the laboratory report. A copy of the reports will be maintained as part of the subject's source documentation.

Details regarding the collection, processing and shipment of samples to an outside lab will be detailed in the Study Procedures Manual, as applicable.

8.4.4.1. HIV, Hepatitis B, and Hepatitis C Testing

A blood sample for diagnostic screening tests for HIV, Hep B and Hep C will be collected at the Screening as indicated in the Schedule of Events (Table 3).

The following diagnostic screening tests will be performed:

- HIV antibodies
- HBsAg
- Hep C antibody
- Hep C PCR analysis

HIV, Hep B, and Hep C analyses will occur at the investigative site's local laboratory.

8.4.4.2. Hematology and Chemistry

A blood sample for hematology and chemistry analysis will be collected at the time points indicated in the Schedule of Events Table 3. Results from labs collected on Day 1 (Visit 2) must be available and reviewed prior to subject's final eligibility review on Day 1 (Visit 2).

A list of the hematology and chemistry tests and parameters to be analyzed is provided in Table 4.

Hematology and chemistry laboratory analyses will be performed at the investigative site's local laboratory. In the event the local laboratory does not perform selected analyses (i.e. direct or indirect bilirubin, anion gap calculation, globulin, RBC indices, or WBC differential for any lineage or by % or abs counts), these will be considered as not required and are recorded as not applicable for that investigative site.

Table 4: Hematology and Chemistry Analysis

Serum Chemistry/Metabolic Panel		
• Albumin • Alkaline Phosphatase Total • Anion Gap • ALT (SGPT) • AST (SGOT) • Urea Nitrogen	• Bilirubin, direct & indirect • Calcium • Carbon dioxide • Chloride • Creatinine • Globulin	• Glucose (fasting not required) • Potassium • Sodium • Total Bilirubin • Total Protein
Hematology/Complete Blood Count with Differential		
• WBC • RBC • Hemoglobin • Hematocrit • Platelet count	RBC Indices: • MCV • MCH • MCHC • RDW	WBC Differential: • Neutrophils, % and abs • Lymphocytes, % and abs • Monocytes, % and abs • Eosinophils, % and abs • Basophils, % and abs

abs = absolute; ALT/SGPT = alanine aminotransferase; AST/SGOT = aspartate aminotransferase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell(s); RDW = red cell distribution width; WBC = white blood cell(s).

Any clinically significant laboratory results, based upon the opinion of the Investigator, identified from the Screening visit labs will be recorded as medical history and should be evaluated against study exclusion criteria (refer to Section 7.2 for additional details).

Abnormal laboratory values which are unexpected or not explained by the subject's clinical condition should be repeated until confirmed, explained or resolved.

8.4.4.3. Urine Pregnancy Test

A urine pregnancy test will be performed at the time points indicated in the Schedule of Events (Table 3) on all female subjects of childbearing potential. Urine pregnancy testing must be performed prior to FCX-007 administration. In the case of a positive pregnancy test, FCX-007 will not be administered.

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

Urine pregnancy testing will occur locally.

8.4.4.3.1. Pregnancy Reporting

The Sponsor or its designee must be notified of any female subject or female partner of a male subject found to be pregnant during the Treatment Period within 24 hours (1 business day) of becoming aware of the pregnancy. The pregnancy should be followed until a final outcome is

known and a final outcome report should be submitted as soon as possible. Generally, follow-up should be no longer than 6 to 8 weeks following the estimated delivery date.

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

8.4.4.4. Bacterial Culture of Wounds

Bacterial cultures may be obtained from wounds at any Treatment Period visit as needed, based upon standard of care and Investigator's judgment, if clinical evaluation is indicative of infection.

Bacterial culture testing will occur at the investigative site's local laboratory.

8.4.4.5. Genetic Testing

A blood sample will be collected at the Screening visit to confirm a genetic diagnosis of RDEB, however, if a subject's RDEB genetic diagnosis has previously been confirmed and results are contained in the subject's medical records, blood sample collection/testing is not required. If testing is required, the results must be available and reviewed prior to subject's final eligibility determination on Day 1 (Visit 2). The following will be reported:

- DNA mutations within COL7A1 gene

RDEB genetic testing will occur at an outside lab.

8.4.4.6. Replication Competent Lentivirus Analysis

A blood sample for RCL analysis will be collected at the time points indicated in the Schedule of Events (Table 3). A blood sample for RCL analysis is not required at Screening if previously performed within the past 2 years and results are contained in the subject's medical records. If RCL analysis was performed >2 years from Screening, a discussion with the Medical Monitor should occur to determine if the testing timeframe is acceptable. Results must be available and reviewed prior to subject's final eligibility determination on Day 1 (Visit 2). If all post-treatment blood RCL assays for an individual subject are negative through one year following the subject's final IP administration (e.g. for those subjects treated in study FI-EB-002, at Week 60 for those who received last injection of FCX-007 at Week 12 or Year 2 for those who received last injection at Week 24 or 36), collection of the yearly follow-up sample may be discontinued for that subject.

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

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

RCL analysis will occur at an outside lab.

8.4.4.7. COL7 Antibody Assay by Indirect Immunofluorescence & Enzyme-Linked Immunosorbent Assay

A blood sample for COL7 antibody assay analysis by IIF & enzyme-linked immunosorbent assay (ELISA) will be collected at the time points indicated in the Schedule of Events (Table 3). A blood sample for COL7 antibody assays is not required at Screening if previously performed within the past 2 years and results are contained in the subject's medical records. If COL7 antibody assay(s) was performed >2 years from Screening, a discussion with the Medical Monitor should occur to determine if the testing timeframe is acceptable. Results must be available and reviewed prior to subject's final eligibility determination on Day 1 (Visit 2).

Subject's serum will be evaluated by IIF using monkey esophagus as a substrate.

If any post-treatment COL7 antibody assay by IIF is newly positive or has a clinically significant increased titer from Screening, a biopsy for DIF will be collected at the subsequent visit (or at an unscheduled visit), as determined by the Investigator. An unscheduled earlier visit may occur as needed.

COL7 antibody assay analysis will occur at an outside lab.

8.4.4.8. Skin Biopsy for Direct Immunofluorescence

A skin biopsy for detection of COL7 antibodies by DIF will be collected at the time points indicated in the Schedule of Events (Table 3) as applicable. The following will be analyzed by DIF:

- Immunoglobulin (Ig) G
- IgA
- IgM
- C3

* At Screening, a biopsy will be collected from the subject's normal/unaffected/intact skin (refer to Appendix 1 for additional collection site guidance). Collection of a skin biopsy for DIF is only required if: 1) subject did not previously have a skin biopsy for DIF performed and results are not contained in the subject's medical records; or 2) the subject was enrolled in a gene therapy trial and did not have a skin biopsy for DIF performed following participation and the results are not contained in the subject's medical records. Screening results must be available and reviewed prior to subject's final eligibility determination on Day 1 (Visit 2).

At subsequent visits, a skin biopsy will be collected if: 1) a treatment wound shows unusual inflammation (beyond temporary inflammation 1-2 days post-injection) suspected to be related to IP, based upon the Investigator's judgment; or 2) a post-treatment COL7 antibody assay by IIF is newly positive or has a clinically significant increased titer from Screening.

The DIF biopsy will be collected from intact/healed skin at or very close to the site of IP administration of the treatment wound that is showing unusual inflammation. The skin biopsy for DIF will be collected from the Second or Third treatment wound rather than the First treatment wound if they show the same pattern of inflammation as the First treatment wound.

If a subject demonstrates a newly positive IIF and no inflammation of the FCX-007 injection sites, the biopsy for DIF will be collected from intact/healed skin at or very close to the site of IP administration from a Second or Third wound if possible, rather than from the First wound.

Biopsy analysis for DIF will occur at an outside lab.

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

8.4.4.9. Skin Biopsy for Hematoxylin and Eosin

A skin biopsy for H&E will be collected as applicable if the area injected with the IP shows unusual growth or inflammation. The H&E report will describe the characteristics of the skin cells and suggest or confirm the diagnosis of the skin condition.

At the specified visits, a skin biopsy will be collected if: 1) the area injected with IP shows unusual growth; or 2) a DIF biopsy is being collected post-treatment and the investigator feels that the H&E biopsy will add additional information to the DIF biopsy.

- If the area injected with the IP shows unusual growth, additional skin biopsies may be necessary to determine the cause of the growth. Skin biopsies for H&E may help to determine if the new growth may be caused by cells that originate in the epidermis or dermis. Additional studies on the biopsies may be necessary as well as additional biopsies in order to confirm the diagnosis. A skin biopsy of the abnormal growth will be collected from the site of the abnormal growth.
- If a DIF biopsy is being collected post-treatment, a skin biopsy for H&E may help determine infection or type of inflammatory reaction. A skin biopsy for this reason will be collected from the area of inflammation or the edge of the area of inflammation.

Biopsy analysis for H&E will occur at the investigative site's local laboratory.

Biopsy collection procedures are provided in Appendix 1.

8.4.4.10. Skin Biopsy for RCL Analysis and/or Insertional Mutagenesis

A skin biopsy may be collected in the area of interest; please contact the sponsor for current procedures.

8.4.4.11. Optional Research Biopsies for Transgene and Vector Persistence

In years 2-6 only (or 1-5 years after the final administration of IP), in a subset of subjects that consent to additional skin biopsy collection, a skin biopsy from the region of FCX-007 investigational gene therapy administration (i.e., treated skin area) may be taken to test for relevant transgene and vector persistence in subjects who consent to the collection of the biopsies required to perform the assay. However, collection of biopsies will stop if transgene and vector persistence is undetected. Please contact the sponsor for current procedures.

8.4.5. Adverse Events

Adverse events will be collected from the time the subject signs the informed consent form (ICF) until the final visit/contact with the subject. At each visit/contact, the Investigator or designee is responsible for reviewing, documenting, and reporting events that meet the definition of an AE.

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

* For any subject who develops an AE suggestive of a retrovirus-associated disease after FCX-007 treatment, attempts will be made to collect any relevant clinical samples for available RCL testing.
* For any subject who dies or is diagnosed with a neoplasm after FCX-007 treatment, attempts will be made to collect a biopsy of the neoplastic tissue or pertinent autopsy tissue to assay for available RCL testing by qPCR.

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

8.4.5.1. Adverse Event Definitions

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

Signs and/or symptoms of the disease under study/lack of efficacy should not be considered as AEs, as long as they are within the normal day-to-day fluctuation or expected progression of the disease. However, significant worsening (e.g., increase in severity or frequency) of the signs and/or symptoms should be recorded as an AE.

- For wounds that are administered IP, the Investigator must monitor the subject's wounds closely for additional blister formation and expansion of the border of the wound during IP injections and immediately post-administration, and at every visit thereafter.
- Any clinically significant change from Screening, based upon the opinion of the Investigator, in physical or examination findings and/or vital signs should be recorded as an AE.

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

Any AE occurring after administration of IP will be considered a treatment-emergent adverse event (TEAE).

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

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

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

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition (e.g., anemia);
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition or if these events meet the criteria as Serious Adverse Events or leads to discontinuation of FCX-007 or from the study;
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE;
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

8.4.5.1.1. Serious Adverse Event

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

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic

bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

- Any event that does not exactly meet this definition yet, in the investigator's opinion represents a significant hazard can be assigned the "important medical events" regulatory reporting serious criteria.

8.4.5.2. Reporting Procedure

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

Each AE requires a complete description including event description (where possible, a diagnosis or if a diagnosis has not been made, individually listed sign(s)/symptom(s)), date of onset and resolution, if applicable, outcome (refer to Section 8.4.5.3), and actions taken to be recorded in the source documents. The Investigator must also assign the following attributes for each AE: its relationship to the IP (refer to Section 8.4.5.4) and severity of the AE (refer to Section 8.4.5.5). The Investigator may be asked to provide follow-up information.

8.4.5.2.1. SAE Reporting Procedure

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

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

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

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

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

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

8.4.5.3. Follow-Up of Adverse Events

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

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

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

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

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

8.4.5.4. Relationship of Adverse Event to Investigational Product

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

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

8.4.5.5. Severity of Adverse Event

The Investigator will make an assessment of the severity of each AE and SAE according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v. 5.0, 2017 (NCI, 2017). The applicable CTCAE version may be updated at periodic intervals during the long-term follow-up period of the study.

For terms not specified in the CTCAE, the criteria in Table 5 should be used to determine the grade severity.

Table 5: Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the NCI CTCAE

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

CTCAE = Common Terminology Criteria for Adverse Events.

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

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

8.5. STUDY ASSESSMENTS AND PROCEDURES BY VISIT

Every effort should be made to adhere to the study assessments and procedures as outlined in the Schedule of Events (Table 3). Additional information about the specific assessments and procedures can be found in Sections 8.2, 8.3, and 8.4.

Supplementary by-visit instructions are presented in this section.

8.5.1. Screening/Wound Monitoring Period

8.5.1.1. Screening (Visit 1)

Screening evaluations may be conducted over multiple visits, however, informed consent must be performed at the first screening visit and collection of biopsies for FCX-007 manufacturing (if not previously obtained) should also be performed at the first screening visit, or as soon as possible thereafter.

Written informed consent must be obtained from the subject and/or their guardian prior to performing any study assessment or procedures (Section 11.3). Provide subject and/or their legal guardian with a copy of the signed and dated consent form (and assent form, if applicable), and document informed consent in the subject's source documents and CRF.

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

The Investigator will view and review the images and measurements of the wounds during the Wound Monitoring Period. In preparation for evaluation of the digital imaging / wound measurement data captured during Wound Monitoring Period should be completed by the Investigator in order to preliminarily identify the potential First, Second, and Third Wound pairs.

8.5.2. Treatment Period

8.5.2.1. Day 1 (Visit 2), Week 12/Month 3 (Visit 3), Week 24/Month 6 (Visit 4), and Week 36/Month 9 (Visit 5)

Prior to FCX-007 administration at Day 1 (Visit 2), subjects will be reassessed to confirm final eligibility to participate in the study.

FCX-007 will be administered to treatment wounds (target wounds randomized to treatment) on Day 1 (Visit 2) and Week 12/Month 3 (Visit 3). At selected clinical study sites only, in a subset of subjects that consent to additional research skin biopsy collection, an additional single treated wound (not from a target wound pair) may be injected with FCX-007.

FCX-007 will be administered to unclosed treatment wounds (target wounds randomized to treatment) on Week 24/Month 6 (Visit 4) and Week 36/Month 9 (Visit 5), and may be administered to unclosed control wounds, per the investigator's discretion.

Post-administration of FCX-007, AEs and concomitant medications should be assessed and recorded, as applicable.

8.5.2.2. Phone Call Assessments

A 3-day post-injection phone call is required following any visit where a subject has received FCX-007 injections.

In addition, phone calls are required midway between visits.

8.5.2.3. Wound Assessment at Week 22

The Blinded Investigator Assessment of the target wounds is expected to be conducted via remote video assessment (telemedicine), assessment of adequate and current (same day) wound imaging, or during a clinic visit.

The Blinded Investigator is only to assess closure of the wound(s) and should instruct the subject or their legal and/ to discuss other issues (e.g., AEs, concomitant medications, visit schedule) with other clinical study personnel.

8.5.2.4. Week 48/Month 12 (Visit 6/End of Treatment)

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

8.5.3. Long-Term Follow-Up

During the long-term follow-up period, the subject and/or their legal guardian, and/or their healthcare provider will be contacted annually to collect information regarding AEs, health changes and relevant concomitant medications (while all concomitant medication use may be reported, the investigator should make every attempt to provide details of concomitant medications used chronically to treat significant diseases or chronic conditions, or any mutagenic medicinal or known exposure to mutagenic agents). Subjects will be encouraged to complete the visit via a remote video visit to allow for the optional efficacy assessment, the Investigator Assessment of Complete Wound Closure.This assessment should occur only for the treated

Target Wound (treatment wound) and not control Target Wound and if the treated Target Wound was closed at Week 48 (Month 12/Year 1) and should cease for further visits if the treated Target Wound is open at any Long-Term Follow-Up visit.

Collection and analysis of a blood sample to monitor for RCL may be performed yearly for up to 15 years. If all post-treatment RCL assays are negative through one year following subject's final IP administration (Week 60 for those who received last injection of FCX-007 at Week 12, or Year 2 for those who received last injection at Week 24 or 36), collection of the yearly follow-up samples may be discontinued.

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

8.5.4. Unscheduled Visit

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

9. TREATMENTS

9.1. TREATMENTS ADMINISTERED

All target wounds (treatment and control wounds) should receive same standard of care wound dressings. Routine skin care for subjects will continue throughout the study.

FCX-007 will be administered intradermally at Day 1 (Visit 2) and Week 12/Month 3 (Visit 3) to the treatment wound(s) only. FCX-007 may also be administered at Week 24/Month 6 (Visit 4) and Week 36/Month 9 (Visit 5) to unclosed treatment wounds and unclosed control wounds, per the investigator's discretion.

At selected clinical study sites only, in a subset of subjects that consent to additional research skin biopsy collection, an additional single treated wound (not from a target wound pair) may be injected with FCX-007 at Day 1 (Visit 2) and Week 12/Month 3 (Visit 3) only.

The IP provided is for use only as directed in this protocol.

9.2. IDENTITY OF INVESTIGATIONAL PRODUCTS

FCX-007 (genetically modified autologous human dermal fibroblasts suspended in Dulbecco's Modified Eagle Medium (DMEM)) is the IP under study. FCX-007 is comprised of autologous fibroblasts isolated from the RDEB subject's skin biopsies and transduced with a virus containing the full-length COL7A1 gene to produce functioning type VII collagen.

9.2.1. FCX-007 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 subject's intact skin. The biopsies will be placed into sterile phosphate buffered saline (PBS), and shipped at 2-8°C overnight to the manufacturing facility. FCX-007 (IP) will be manufactured from the biopsies obtained at the Screening Visit, if not previously obtained in the prior FCX-007 study (i.e., FI-EB-001).

Upon receipt of the biopsies, the tissue will be digested with enzymes to release the fibroblast cells, 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 to obtain a sufficient quantity of Drug Substance material for study treatment, and are then cryopreserved. Cells undergo Drug Substance release testing prior to initiating Drug Product (DP) manufacturing. Released Drug Substance vials are thawed and expanded over a short period of time to create sufficient material for DP preparation.

If the manufacturing process does not meet manufacturing release specifications, an additional set of biopsies may be requested from the subject.

The duration between biopsy collection and completion of manufacturing is approximately 4-6 months but can vary due to capacity and technical manufacturing reasons.

9.3. PACKAGING, LABELING, SHIPPING, STORAGE AND HANDLING

9.3.1. Packaging

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

It is intended that 15 vials of FCX-007 will be provided per subject for each treatment session, as applicable (60 vials total for 4 treatment sessions).

9.3.2. Labeling

The vials and secondary packaging will be labeled and will include the following information for US sites, with appropriate adaptations for other North American sites (per regulatory requirements):

- *Sponsor Name:* Castle Creek Biosciences
- *IP Name/Volume:* FCX-007 (GM-HDF-COL7) 1 mL
- SIN # *(Subject Identification Number)* / Initials / DOB *(Date of Birth)*:
- Lot #:
- Expiration Date / Time: by US Eastern Time
- Nominal Conc.: 2e7 cells/mL
- Store at 2-8°C
- CAUTION: NEW DRUG – Limited by Federal (or United States) Law to Investigational Use
- NOT EVALUATED FOR INFECTIOUS SUBSTANCES

9.3.3. Shipping

After Drug Substance manufacturing is complete and released, the Sponsor or its designee and the Investigator will mutually agree on the date of receipt of FCX-007 IP for all treatment sessions.

FCX-007 will be packaged in refrigerated temperature controlled and monitored shippers and shipped for same day or overnight delivery to the investigative site.

9.3.4. Storage and Handling

Upon receipt of the shipper containing FCX-007 IP vials, the investigative site will perform a series of tasks to ensure the IP product arrived in its intended state. IP vials must be kept in the shipper until ready for use, within 48 hours of the IP vial fill time.

* FCX-007 must be fully administered prior to the expiration date and time indicated on the product label.

9.4. INVESTIGATIONAL PRODUCT ACCOUNTABILITY

The Investigator or designee is responsible for ensuring accurate accountability records of all used and unused IP. Upon receipt of IP, the Investigator or designee will conduct a complete inventory of all IP received and assume responsibility for its appropriate storage, handling, and use. The Investigator or designee is responsible for ensuring all IP is accounted for and appropriately inventoried and receipt of each shipment of IP (quantity and condition), administration records and final accountability of IP is appropriately documented. Drug accountability records of all IP received and administered or unused must be maintained and readily available for inspection by the site monitor, auditor and/or regulatory authorities at any time.

Investigational product and associated documentation will be periodically reviewed and verified by the site monitor over the course of the study.

9.4.1. Disposal

Arrangements will be made for used and unused IP to be destroyed on site or returned to Castle Creek following acceptable, documented procedures. Further guidance and information for final disposition of used and unused IP will be provided.

After administration, all empty, partially used, and unused vials must be retained for product accountability, if allowable per site guidelines. These vials can be disposed of after final reconciliation is performed by the site monitor.

9.5. WOUND RANDOMIZATION

This study will not have a separate control group. Randomization of target wounds in each target wound pair to either FCX-007 treatment (treatment wound) or untreated control (control wound) will be independently assigned on Day 1 (Visit 2) following target wound labeling and pairing into target wound pair(s).

Prior to the end of Wound Monitoring Period for the first subject, randomization codes for each subject's target wound pairs (First, Second, and Third Wound Pairs) assigning each target wound within the target wound pair(s) to either FCX-007 treatment (treatment wound) or untreated control (control wound) will be generated by the study biostatistician. The full randomization list will be retained by an independent statistical group. The randomization codes will be provided to the investigative site in sealed envelopes. The randomization envelope for a subject, available only to limited site personnel, will not be opened until the First, Second, and Third Wound Pairs are selected for that subject (refer to Section 8.3.1.2 for additional details).

9.6. INVESTIGATIONAL PRODUCT DOSING

FCX-007 will be administered intradermally at Day 1 (Visit 2) and Week 12/Month 3 (Visit 3) to the treatment wound(s). FCX-007 may also be administered at Week 24/Month 6 (Visit 4) and Week 36/Month 9 (Visit 5) to unclosed treatment wounds and unclosed control wounds, per the investigator's discretion.

At selected clinical study sites only, in a subset of subjects that consent to additional research skin biopsy collection, an additional single treated wound (not from a target wound pair) may be injected with FCX-007 at Day 1 (Visit 2) and Week 12/Month 3 (Visit 3) only.

Table 6 provides details regarding the number of cells, vials and injections per treatment session.

Table 6: FCX-007 Cell Count, Vials and Injections per Treatment Session

FCX-007 Cells:	Up to 450 million
Concentration of FCX-007 Suspension:	10 to 30 million cells/mL
# Vials:	Up to 15
Injections per Vial:	4 (each injection 0.25 mL)
Cells per Injection:	2.5 to 7.5 million
Number of Injections:	Up to 60

9.7. INVESTIGATIONAL PRODUCT ADMINISTRATION

Subjects will receive intradermal injections of FCX-007 into the superficial papillary dermis in each specified treatment wound in two or more treatment sessions. Intradermal injections of FCX-007 0.25 mL will be administered at approximately 1 cm intervals around, and within 1 cm of, the perimeter of the treatment wound(s) and across the wound (or healed wound bed, when applicable) (refer to Figure 4 and Figure 5); a maximum of 15 mL (in 60 injections) may be administered per session, and the Investigator is encouraged to administer the full quantity of FCX-007 should the total wound size permit. As the wound size and shape will dictate the quantity of FCX-007 to be administered, it is not possible to calculate this until after randomization. As a general rule, the maximum number of injections of FCX-007 is expected to be used over a surface area of approximately 60- 80 cm^2.

* If possible, each treatment wound will receive the same amount and number of injections of FCX-007 during each of the first 2 treatment sessions (e.g., treatment wound labeled T1B receives 4.5 mL of FCX-007 in 18 injections at Day 1 (Visit 2) and at Week 12/Month 3 (Visit 3)). This may not be possible if a wound has expanded in size or under other clinical circumstances.

The first treatment session occurs at Day 1 (Visit 2) and the second at Week 12/Month 3 (Visit 3). At these visits, the treatment wound in the First Pair will be injected first, followed sequentially by the Second and Third Pairs (if applicable, and only as sufficient product is available). It is permissible for a treatment wound in the Second or Third Pair to be partially treated due to insufficient quantity of product, if the treatment wound in the First or Second Pair was completely treated.

At selected sites only, in a subset of subjects that consent to additional research skin biopsy collection, an additional single treated wound (not from a target wound pair) may be injected with FCX-007 at Day 1 (Visit 2) and Week 12/Month 3 (Visit 3) only.

Additional treatment sessions may occur at Week 24/Month 6 (Visit 4) and Week 36/Month 9 (Visit 5) when unclosed treatment wounds may be re-treated, and unclosed control wounds may be treated.

Administration of FCX-007 will not occur in a specific treated wound if: 1) a treated wound shows unusual inflammation (beyond temporary inflammation 1-2 days post-injection) suspected to be related to the IP, based upon the Investigator's judgment; or 2) an area injected with IP shows unusual growth.

Subjects will be administered anesthesia per standard of care at the investigative site. To minimize pain and discomfort during the IP 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 (e.g., lorazepam).

Refer to Appendix 3 for detailed instructions regarding the administration of IP.

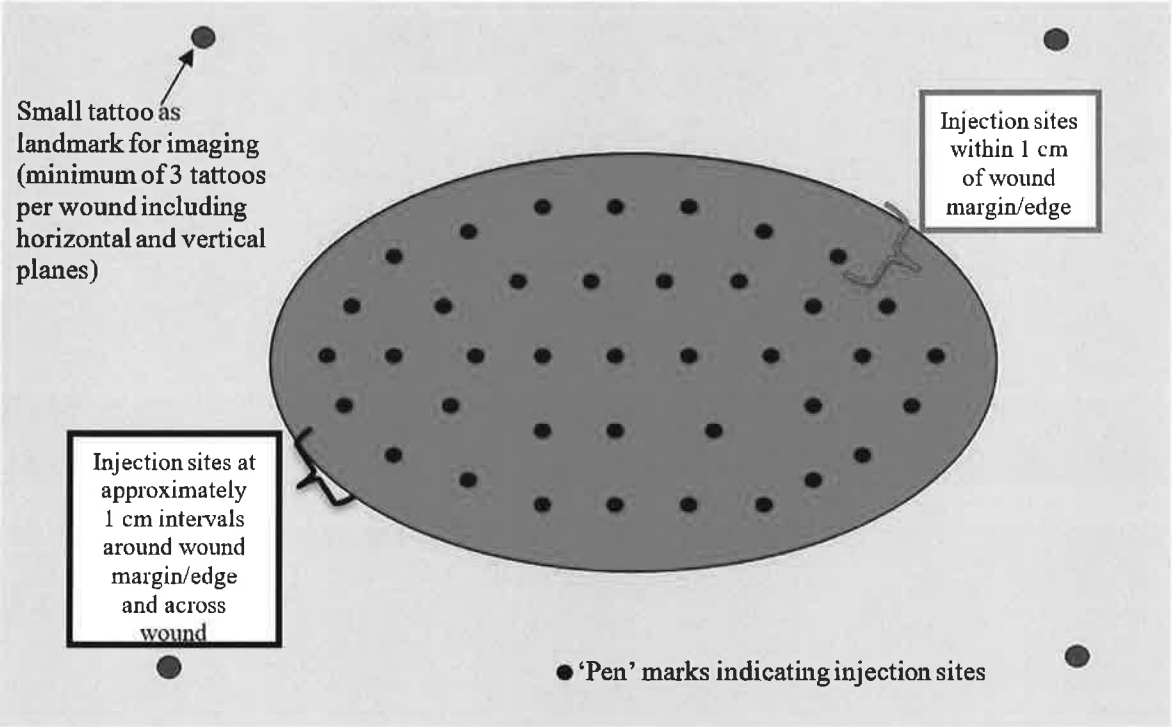
9.7.1. FCX-007 Administration Preparation

Prior to FCX-007 administration:

1. Confirm identification of First, Second, and Third Wound Pairs (refer to Section 8.3.1.2 for additional details) and the target wounds within the pairs that have been randomized to treatment (treatment wounds).
2. At Day 1 (Visit 2), small tattoos may be placed on non-blistered skin near target wounds (both treatment and control) as a landmark for imaging and to aid in the assessment of the target wound margins/edges as necessary (refer to Figure 3).
    - At subsequent visits, small tattoos may be placed again at sites previously tattooed at Day 1 (Visit 2) on non-blistered skin near the target wounds (both treatment and control) if previously placed tattoos are faded.
3. Take images of each treatment and control wound after tattoos are placed, as applicable.
4. After tattooing as applicable, and images are taken, a surgical marker will be used to make the following marks on each treatment wound.
    - Using a sterile ruler, place dots at the injection sites at approximately 1 cm intervals around, and within 1 cm of, the perimeter of the First treatment wound, and across the wound (or healed wound bed) in a grid pattern.
    - For a Second or Third wound in which there is insufficient amount of product remaining to administer at the entire perimeter of the wound and across the wound, the perimeter should be treated first.
5. Count each injection site mark to know the precise number of injections that will be administered to each treatment wound.

Figure 4 diagrams the injection pattern of a completely treated wound with markings.

Figure 4: Treatment Wound – Investigational Product Administration Preparation Markings



9.8. TREATMENT COMPLIANCE

FCX-007 is administered by the Investigator and records of administration are to be maintained at the site and will be recorded in the subject's source documents and CRF. Subjects will be monitored for adherence to the schedule for FCX-007 administration.

9.9. PRIOR AND CONCOMITANT MEDICATIONS/TREATMENTS

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

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

Throughout the study, any concomitant medications/treatments deemed necessary to provide adequate supportive care may be prescribed. In particular, medication should be considered during and after the FCX-007 injections to treat pain and/or anxiety (e.g., lorazepam).

The name of the medication (generic name), indication/reason for use, dose, frequency, administration route, and dates of the first and last dose, as applicable, will be recorded in the subject's source documents and CRF.

During the long-term follow-up period, while all concomitant medication use may be reported, the investigator should make every attempt to provide details of concomitant medications used chronically to treat significant diseases or chronic conditions, or any mutagenic medicinal or known exposure to mutagenic agents.

The Medical Monitor should be contacted if there are any questions regarding prior or concomitant medications/treatments.

9.9.1. Skin/Wound Care Regimen

There are no restrictions on skin/wound care however, all target wounds (treatment and control wounds) should receive same standard of care from Day 1 through Week 48, if at all possible (ideally, also during the Screening period). Subject's skin/wound care regimen will be reviewed and recorded at Screening and reviewed/updated at every visit.

Routine skin/wound care for subjects will continue throughout the study.

9.9.2. Birth Control Requirements

Female subjects of childbearing potential and fertile male subjects who are engaging in sexual activity that could lead to pregnancy must use at least 1 of the following adequate birth control regimens while in the study and for 6 months after the last dose of FCX-007 is administered.

- Male partner with vasectomy, OR
- Male condom AND partner use of one of the contraceptive options below:
  - Spermicide
  - Intrauterine device or intrauterine system
  - Oral contraceptive, either combined or progestogen alone
  - Contraceptive subdermal implant (e.g., Norplant®)
  - Injectable progestogen (e.g., Depo-Provera®)
  - Contraceptive vaginal ring (e.g., NuvaRing®)
  - Transdermal contraceptive patches (e.g., Ortho Evra®)
- Subjects of childbearing potential who are abstinent are eligible, but they must agree to use one of the birth control regimens listed above if they begin engaging in sexual activity that could lead to pregnancy during the study.
- Periodic abstinence e.g., calendar, ovulation, sympto-thermal, post-ovulation methods and withdrawal are not acceptable methods of contraception.

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

9.9.3. Prohibited Medications/Treatments and Nondrug Therapies

The use of any of the following are prohibited during this study (Screening through Week 48/Month 12 (Visit 6)):

- Other investigational EB medications/treatments or procedures
- Chemical or biological intervention for the specific treatment of RDEB
  - Topical chemical agents *with the exception of biological or gene therapy* based agents may be applied to wounds that are ineligible for inclusion in the study as part of the assigned paired wounds (treated or untreated) or an optional treated wound for biopsies. If use of such topical agents are anticipated or planned, they should be applied consistently throughout the observation period prior to initiating study treatment and throughout the treatment period. Wounds that are treated with these topical agents should be clearly distinguishable from wounds in assigned pairs. The topical agent should be recorded as a prior/concomitant medication, and notation should be made in the indication statement that this was not applied to study wounds.
- Chemotherapy (other than topical products for cutaneous pre-cancerous or cancerous lesions); every effort should be made to refrain from use at selected Target Wound pairs
- Other investigational drug

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

10. STATISTICAL METHODS PLANNED

10.1. GENERAL CONSIDERATIONS

The objective of this Phase 3 study is to show that FCX-007 safely leads to convincing clinically significant improvement in wound healing in children, adolescents, and adults with RDEB.

Each subject will serve as their own control as target wounds will be randomly assigned as the treatment wound (FCX-007 is administered) or control wound.

10.2. SAMPLE SIZE DETERMINATION

Based on observed Phase 1/2 study data, 60% wound closure in treated wounds, and 10% wound closure in control wounds is assumed, with a total discordance of 70%. A sample size of 24 provides 85% power at a significance level of 0.05 to detect a difference of 50% between treated and control wounds when there are 70% discordant pairs, using a McNemar's test. All calculations were performed with PASS 2020 v20.0.2.

10.3. ANALYSIS POPULATIONS

10.3.1. Full Analysis Set

The primary population for analysis of efficacy is the full analysis set (FAS). The FAS population includes subjects who were administered FCX-007.

10.3.2. Per-Protocol

The per-protocol (PP) population is defined as all subjects in the FAS who complete the Weeks 22 and 24 assessments within the specified visit windows, and who do not meet any of the following criteria:

- Did not receive intradermal injections of FCX-007 in the treated First Wound at Baseline and Week 12;
- Other significant protocol violations, including medically significant violations of inclusion/exclusion criteria or prohibited medications/treatments which may reasonably affect wound healing.

Analyses using the PP population will be considered supportive.

10.3.3. Safety

The safety population includes subjects who were administered FCX-007.

10.4. PLANNED ANALYSES

This section briefly describes the planned statistical analysis. A Statistical Analysis Plan (SAP) will be written that provides specific details of these analyses and will be finalized prior to database lock. In case the language in this section differs from the language in the SAP, the SAP is considered operative.

Statistical analyses will be performed using 2-sided tests at a Type I error rate of 0.05. The secondary outcomes will only be formally tested if the primary outcome is statistically significant.

Data will be summarized by treatment regimen and, when applicable, by study visit. Descriptive statistics including counts and percentages for categorical data; and n (number of subjects), mean, standard deviation (SD), median, minimum and maximum 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 and related percentages.

The SAP will specify the details of the analyses to be used for the efficacy, safety, and supportive analyses, including methods for missing data. All data listings, summaries, figures, and statistical analyses will be generated using SAS version 9.4 or higher or other validated software.

10.4.1. Baseline Descriptive Characteristics

The numbers of subjects in each analysis population will be summarized by treatment group.

The descriptive summaries of subjects' demographic and baseline characteristics will be presented by treatment group. 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.

10.4.2. Efficacy Analyses

10.4.2.1. Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is complete wound closure of the First Wound Pair at Week 24, with confirmed complete wound closure at serial assessments at Weeks 22 and 24.

The method of analysis will be logistic regression using a compound symmetry covariance structure.

10.4.2.2. Secondary Efficacy Endpoint Analyses

The first secondary endpoint, complete wound closure of the First Wound Pair at Week 12, will be analyzed similarly to the primary endpoint.

The remaining secondary endpoints will be analyzed similarly to the primary endpoint, with consideration of the repeated measurements within subjects.

The secondary endpoints will only be tested if the primary endpoint is significant. Testing of the secondary endpoints will follow a gated sequential approach. Once the primary endpoint demonstrates statistical significance, the secondary endpoints will be tested in the given order, with testing of each endpoint proceeding only if the preceding endpoint reaches statistical significance.

10.4.2.3. Supportive Efficacy Endpoint Analysis

Supportive efficacy endpoints will be summarized. Any testing of the supportive efficacy endpoints will be done for exploratory purposes only; no adjustment for multiplicity will be made.

10.4.3. Safety Analyses

All continuous parameters will be summarized using standard summary statistics as appropriate (number, mean, SD, median, minimum, maximum). Summary statistics for categorical variables will include frequency counts and percentages. Premature termination will be tabulated and summarized.

Safety evaluations will be based on occurred AEs, laboratory values, vital signs and appearance of COL7 autoantibodies, and RCL.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Severities of toxicities will be described using the NCI CTCAE grades. Adverse events will be grouped into pre-treatment AEs and TEAEs and will be tabulated by preferred terminology and by body system for each study phase. The number of AE entries, as well as the number of subjects will be reported. Analyses will include tabulation of AE type, relationship to FCX-007, seriousness, and severity of AEs according to CTCAE.

Laboratory test values will be presented in shift tables and by display of changes to baseline. Evaluations of COL7 autoantibodies and RCL will be done descriptively.

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

10.5. SENSITIVITY ANALYSES

Sensitivity analyses will be included in order to assess the impact of missing data.

In the event that the FAS population does not represent a conventional intent-to-treat population, including all subjects with randomized First Wound Pairs, sensitivity analyses to evaluate the consistency of the results between these populations will be performed.

10.6. INTERIM ANALYSES

There will be no formal interim analysis.

10.7. HANDLING OF MISSING DATA

Every effort will be made to collect complete data at all visits.

The SAP will detail methods for missing values. The primary method of handling data will be last observation carried forward (LOCF).

Standard clinical monitoring and data management practices will be used to ensure the integrity of data.

11. ETHICS AND GENERAL STUDY CONDUCT CONSIDERATIONS

11.1. ETHICAL CONDUCT OF THE STUDY

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

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

11.2. INSTITUTIONAL REVIEW BOARD

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

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

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

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

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

11.3. SUBJECT INFORMATION AND CONSENT

11.3.1. General Provisions

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

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

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

The Investigator or designee is responsible for obtaining written informed consent/assent from the subject or legally authorized representative (see note below) before any protocol-specific procedures are performed.

Informed consent/assent will be obtained after a full explanation of the purpose of the study, risks and discomforts involved, potential benefits, etc. have been provided in both oral and written form. The subject or the subject's legally authorized representative must be given ample opportunity to inquire about details of the study. The ICF/Assent that is used must be the current IRB approved version and must be signed and personally dated by the subject or a legally authorized representative and by the person who obtained the consent (not necessarily an investigator).

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

For children and adolescent subjects, the Investigator is responsible for obtaining informed consent from the subject and/or their legal guardian and assent from the subject as required by the approving IRB and local requirements.

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

The acquisition of informed consent/assent should be documented in the subject's medical records. A copy of the signed consent form (and assent, if applicable) must be provided to the subject or legally authorized representative and the original will be maintained with the subject's records.

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

11.3.2. Assent

As required by the approving IRB and local requirements, assent from a subject will also be obtained. The approving IRB should address whether the intended subject population of children would be capable of understanding the nature of their participation in the research, and if so, whether or how assent will be obtained. In determining whether a child is capable of providing assent, the IRB must take into account the ages, maturity, psychological state and intellectual and emotional ability of the child to comprehend the concepts involved in the assent process. This judgment may be made for all children to be involved in clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate. In general, assent is usually obtained from a child ≥7 years of age.

11.3.3. Children Reaching the Legal Age of Consent During the Study

Due to the long-term nature of this study, a child who was enrolled in this study with parental or guardian permission, may reach the legal age of consent. Unless the IRB determines that the requirements for obtaining consent can be waived, the investigator or designee will need to obtain informed consent for the now-adult subject for any ongoing interactions or interventions with the subject for this study.

11.4. PROTOCOL COMPLIANCE

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

11.5. CHANGES TO THE PROTOCOL

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

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

11.6. POSTING OF INFORMATION ON PUBLICLY AVAILABLE CLINICAL TRIAL REGISTERS

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

11.7. STUDY DOCUMENTATION

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

11.7.1. Investigator Study File

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

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

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

11.7.1.1. Subject's Source Documentation

The Investigator must maintain detailed and accurate records (other than the CRF) on all study subjects. The subject's source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to the original signed/dated informed consent/assent, HIPAA authorization, hospital records, clinical and office charts, laboratory/diagnostic testing results, pharmacy/drug accountability records, diaries, microfiches, radiographs, photographs and correspondence. Telephone conversations with the subject, subject's legal authorized representative and/or the Sponsor or its designee concerning the subject must also be recorded and retained.

11.7.1.2. Pre-Study Documentation Requirements

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

- Signed and dated investigational brochure (IB) receipt form
- Signed and dated protocol signature page (Investigator's Agreement)
- A blank copy of the IRB-approved ICF (and assent documents, if applicable)
- Copy of the IRB approval of the protocol, information letter, consent form, and assent form, as applicable
- Completed FDA Form 1572 (if applicable). Local laboratories, laboratories providing endpoint data and any central laboratories for the study must be listed on the form.

- Up-to-date curriculum vitae or equivalent for each person listed on the Form FDA 1572 (if applicable) or applicable similar document
- Signed Financial Disclosure Form for each person listed on the Form FDA 1572 (if applicable) or applicable similar document
- IRB membership list
- The IRB composition and/or written statement that IRB is in compliance with regulations
- Local laboratory(ies) normal ranges
- Documentation of the local laboratory(ies) certification/licenses (e.g., CAP/CLIA or other) or equivalent
- A fully executed Clinical Trial Agreement

11.8. DATA COLLECTION, MANAGEMENT, MONITORING, AND RETENTION

11.8.1. Data Collection and Management

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

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

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

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

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

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

11.8.1.1. Subject Confidentiality

The investigator must take all reasonable measures to ensure that the subject's confidentiality is maintained. Study subjects will not be identified by name in the study database or on any study

documents to be collected by the Sponsor or its designee. On the CRFs or other documents submitted to the Sponsor and those working with the Sponsor, subjects should be identified by their initials, DOB as applicable, site number, study subject number, and/or unique clinical identification number as applicable only. The Investigator must keep a log showing study subject numbers, names, and addresses for all subjects enrolled in the trial. Documents that are not for submission to the Sponsor or those working with the Sponsor should be kept in strict confidence by the Investigator.

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

11.8.1.2. Data Quality Control and Reporting

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

11.8.2. Monitoring/Auditing

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

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

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

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

11.8.3. Retention of Records

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

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

11.9. FUTURE USE OF STORED SPECIMENS AND DATA

With the subject's approval, biopsy specimens obtained for the manufacture of FCX-007 may be used in the future for manufacturing process development research and/or for future manufacturing of DP for use by the subject in future clinical trials or following FCX-007 commercialization, if applicable.

11.10. PUBLICATION POLICY

The information provided in support of or generated as a result of this study is confidential. Any use or reproduction thereof, including but not limited to publications or presentations by the Investigator or their 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.

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13. APPENDICES

13.1. APPENDIX 1: BIOPSY COLLECTION PROCEDURES

BIOPSY SUPPLIES

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

- Punch biopsy instruments
- Biopsy vials containing appropriate media, as applicable
- Associated documentation, as applicable
- Shipping materials, as applicable

Prior to the procedure, the Investigator or designee 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

COLLECTON SITES

A high-level overview of when biopsies may be collected and collection sites is provided below (refer to Sections 8.2.3, 8.3.4, 8.4.4.8, and 8.4.4.9 for specific details of when biopsies are collected and associated collection sites).

<table>
<tr><th>Biopsy</th><th>Screening/ Baseline</th><th>Week 24/Month 6 (V4)</th><th>Week 36/Month 9 (V5)</th><th>Week 48/ Month 12 (V6) or EOT</th></tr>
<tr><td>Biopsies for FCX-007 Manufacturing</td><td rowspan="2">Normal/ Unaffected/ Intact Skin</td><td>NA</td><td>NA</td><td>NA</td></tr>
<tr><td>Biopsy for DIF (if necessary)</td><td colspan="3">Performed if applicable in treatment wound– from area of inflammation or the edge of area of inflammation, or at or close to the site of IP Administration if performed due to positive COL7 antibody</td></tr>
<tr><td>Biopsy for H&E (if applicable)</td><td>NA</td><td colspan="3">Performed if applicable in treatment wound– from site of abnormal growth or from area of inflammation or the edge of area of inflammation</td></tr>
<tr><td>Biopsy for IEM (if applicable)</td><td rowspan="2">Normal/ Unaffected/ Intact Skin</td><td colspan="3" rowspan="2">Treated Wound (unpaired) – from intact/healed skin at or very close to site of IP Administration</td></tr>
<tr><td>Biopsy for IF (if applicable)</td></tr>
</table>

Guidance for Biopsies Collected from Subject's Normal/Unaffected/Intact Skin:

- For biopsies that are to be collected from the subject's normal/unaffected/intact skin, the specific location will vary on a case-by-case basis based on the Investigator's judgment. 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, the anatomical locations including upper leg, calf, trunk and upper arms (in descending order of frequency) are recommended areas.

COLLECTION PROCEDURE

***Premedication/Local Anesthesia**

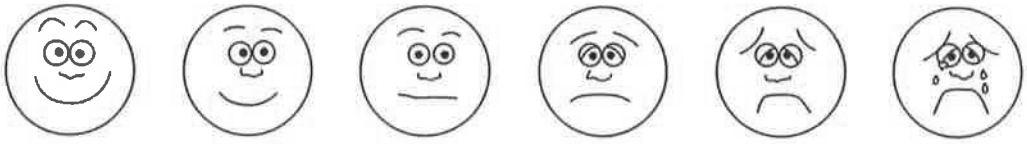
All biopsies are obtained after anesthesia. Investigators should employ standard practice to locally anesthetize the biopsy areas. It is anticipated that a topical lidocaine or lidocaine / prilocaine cream will be followed by a 1% lidocaine with epinephrine (10 mg/mL with epinephrine) injection. In addition, premedication to treat anxiety (e.g., lorazepam) should be considered. All medications used must be recorded in the subject's source documents and CRF.

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

13.2. APPENDIX 2: WONG-BAKER FACES® PAIN RATING SCALE

Instructions for Use

Wong-Baker FACES® Pain Rating Scale



0	2	4	6	8	10
No Hurt	Hurts Little Bit	Hurts Little More	Hurts Even More	Hurts Whole Lot	Hurts Worst

Instructions for Usage

Explain to the person that each face represents a person who has no pain (hurt), or some, or a lot of pain.

Face 0 doesn't hurt at all. Face 2 hurts just a little bit. Face 4 hurts a little bit more. Face 6 hurts even more. Face 8 hurt a whole lot. Face 10 hurts as much as you can imagine, although you don't have to be crying to have this worst pain.

Ask the person to choose the face that best depicts the pain they are experiencing.

13.3. APPENDIX 3: INVESTIGATIONAL PRODUCT ADMINISTRATION INSTRUCTIONS

Intradermal injections of IP are to be administered by the PI or, if necessary, an appropriately trained physician Sub-I.

1. Premedicate/Administer anesthesia.
    - Subjects will be administered anesthesia per standard of care at the investigative site. To minimize pain and discomfort during the IP administration, the 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 (e.g., lorazepam).
2. Perform the FCX-007 Administration Preparation procedures (refer to Section 9.7.1).
3. Approximately 15 minutes prior to the administration of FCX-007, remove the subject's treatment vials from the shipper.
4. Resuspend the cells by gently inverting the injection vial three (3) times.
5. Tap the top of each vial to release any fluid in the cap prior to opening the vials. Do not dilute the product.
6. Unscrew the cap and, using a detachable bore (such as 21-gauge needle, or the hub of the sterile syringe), aseptically draw 1.0 mL from one vial. 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.
7. Once the product is in the syringe, remove the 21-gauge needle, if applicable, 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.
8. 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 syringe arms, placing the thumb on the upper arm of the syringe. Do not place the thumb on the plunger while directing the needle into the skin to avoid premature discharge of the product.
9. Insert the 30-gauge needle at the pre-identified and marked injection site.
10. Introduce the needle into the superficial papillary dermis and bring the needle along a line parallel to the wound margin/edge (refer to Figure 5). **The shadow or impression of the barrel of the needle under the skin should be perceptible if the injection 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.*
11. The graduated markings on the syringe should be visible to ensure that the correct amount is being injected.

12. 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.
    - 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.**
13. Remove needle then insert needle at next mark and repeat steps 12 through 13 to complete all planned injections of FCX-007.
    - Syringes will be changed after every 4 injections (0.25 mL per injection) since each syringe will contain 1.0 mL of FCX-007

Figure 5: Photographs of Intradermal Injection of FCX-007