STATISTICAL ANALYSIS PLAN

Protocol Number:	FI-EB-002
Study Title:	A Pivotal Phase 3 Study of FCX-007 Genetically-Modified Autologous Human Dermal Fibroblasts) for Recessive Dystrophic Epidermolysis Bullosa (DEFI-RDEB)
Development Phase of Study:	3
Sponsor:	Castle Creek Biosciences
Sponsor Contact:	[redacted]
Statistical Analysis Plan based on Protocol Version:	V5.1 (04May2022)
Statistical Analysis Plan Date:	29Sep2022
Statistical Analysis Plan Version:	V3

SAP Approval

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Revisions to the Statistical Analysis Plan described herein must be approved through a formal written amendment with the exception of minor editorial changes to tables, figures, or listing shells, and any necessary textual clarifications for programmers that do not affect the stated analysis variables, study endpoints, or statistical methods.

SAP Change History

Version	Date	Summary of Changes	Author
2	23Dec2020	Original document corresponding to Protocol Version 3 (09Oct2020)	[redacted]
3	29Sep2022	Updates to remove statistical testing due to decrease in sample size.	[redacted]

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abond	Abond CRO, Inc.
AE(s)	adverse event(s)
AF(s)	anchoring fibril(s)
ATC	anatomical therapeutic chemical
BMZ	basement membrane zone
cm	centimeter
COL7A1	type VII collagen gene
COL7	type VII collagen protein
CRF(s)	case report form(s)
DSMB	Data Safety Monitoring Board
EB	epidermolysis bullosa
eCRF(s)	electronic case report form(s)
FAS	full analysis set
FDA	Food and Drug Administration
IEM	immunoelectron microscopy
IF	immunofluorescence
LOCF	last observation carried forward
LSMean or LSM	least square mean
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
mL	milliliter
n	number of observations
N	number of subjects (sample size)
PI(s)	principal investigator(s)
PT	preferred term
RCL	replication-competent lentivirus
RDEB	recessive dystrophic epidermolysis bullosa
SAE(s)	serious adverse event(s)
SAS®	Statistical Analysis System (SAS® Institute Inc., Cary, NC)
SCC	squamous cell carcinoma
SD	standard deviation
SoC	standard of care

SOC	system organ class
sub-I(s)	Sub-Investigator(s)
TEAE(s)	treatment-emergent adverse event(s)
WA	wound assessment
WHO	World Health Organization
WHO-DDE	World Health Organization Drug Dictionary

2. INTRODUCTION

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 a clinically severe variant, recessive dystrophic epidermolysis bullosa (RDEB) [1].

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 [2].

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 esophageal involvement [3]. 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 ([4]; [5]; [6]); 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 [5]. 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 [6].

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 ([7]; [8]; [9]; [10]). 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, Fibrocell 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.

3. STUDY OBJECTIVES

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.

4. STUDY DESIGN

4.1 Overall Study Design

DEFI-RDEB is a multi-center, intra-subject 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 potential target wounds with a minimum 12-week Wound Monitoring Period (through photography). 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.

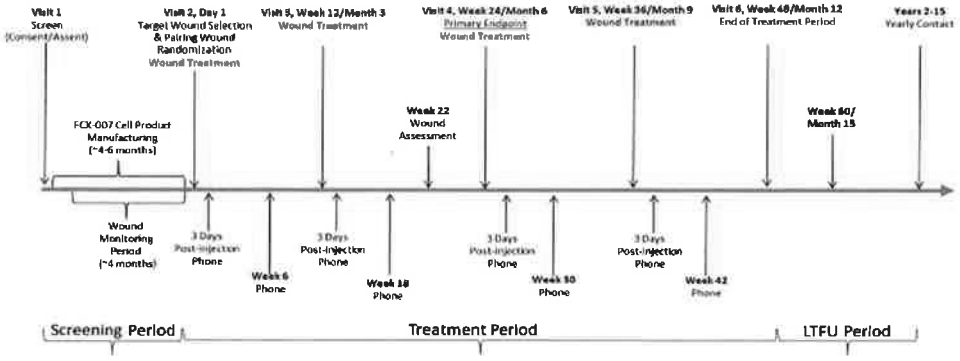
The first treatment session occurs at Day 1 (Visit 2) and the second at Week 12/Month 3 (Visit 3). At these visits, the treatment wound in the First Pair will be injected first, followed sequentially by the Second and Third Pairs (if applicable, and only as sufficient product is available). It is permissible 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 (through 15 years) commences for subjects who have received one or more FCX-007 injections of any volume.

The study schema is presented below.



4.1.1 Schedule of Visits and Assessments

Refer to Table 3 within the Protocol for the Schedule of Events.

4.1.2 Method of 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 Abond. 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 Protocol Section 8.3.1.2 for additional details).

4.1.3 Blinding

Screening and Baseline wound assessments (WAs) necessary for identification, mapping, selection, and labeling are to be performed by the PI, or trained, medically qualified Sub-Investigator (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 Weeks 12, 22, and 24 (Table 3 of protocol). Blinded assessment is also preferred at Weeks 36 and 48. 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.

5. EFFICACY AND SAFETY ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoints

The primary efficacy endpoint is:

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

5.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- 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

5.1.3 Supportive Efficacy Endpoints

The supportive efficacy endpoints are as follows:

- 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

5.2 Safety Endpoints

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

6. STATISTICAL AND ANALYTICAL PLANS

6.1 General Methodology

All statistical processing will be performed using SAS® unless otherwise stated. No interim analyses are planned. The primary analysis will occur once all subjects have completed Week 24. No statistical testing will be performed.

Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented. For continuous parameters, descriptive statistics will include n (number of subjects), mean, standard deviation (SD), median, minimum and maximum.

The primary method of handling missing efficacy data will last observation carried forward (LOCF).

Efficacy analysis will be performed on the Full Analysis Set (FAS) population.

The number of subjects in each analysis set will be summarized. Reasons for study withdrawal during the treatment period will be summarized using frequencies and percentages.

Reported AEs, medical history terms and prior and concomitant procedures and therapies will be classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology. Prior and concomitant medications will be classified on the basis of World Health Organization Drug Dictionary (WHO-DDE) terminology.

6.1.1 Statistical Analysis

All analyses will be performed by Abond CRO using SAS® Version 9.4 or later. All summary tables and data listings will be prepared utilizing SAS® software.

The standard operating procedures (SOPs) of Abond will be followed in the creation and quality control of all data displays and analyses.

6.1.2 Baseline Definition

Baseline is defined as the last non-missing assessment prior to first injection. For the primary endpoint, baseline refers to Day 1 (pre-initial injection) images, measurements and assessments.

6.1.3 Visit Windowing

Data will be summarized based on nominal visit indications with the exception of data captured at early termination and unscheduled visits; data from early termination and unscheduled visits will be summarized based on mapped visit values. The analysis windows for early termination and unscheduled visits are presented in the following table.

Analysis Windows for Early Termination and Unscheduled Visit Mapping

Scheduled Visit	Protocol Specified Window	Analysis Window
Week 12	Week 11 to 16 (Day 78 to 113)	Week 6 to 18 (Day 43 to 126)
Week 24	Week 23 to 28 (Day 162 to 197)	Week 18 to 30 (Day 127 to 210)
Week 36	Week 35 to 40 (Day 246 to 281)	Week 30 to 42 (Day 211 to 294)
Week 48	Week 47 to 52 (Day 330 to 365)	Week 42 to 54 (Day 295 to 379)

Early termination and unscheduled visits will not be mapped to the Week 22 visit.

Data collected at early termination and unscheduled visits prior to study day 78 will not be analyzed, with the exception of those identified as baseline values. Data from assessments performed after study day 379 will not be included in analyses.

The definition for the study day included in each study window is defined as below:

Study Day prior to Day 1 = Visit Date – Day 1 Date

Study Day on or after Day 1 = Visit Date – Day 1 Date + 1

If an assessment's mapped visit is a visit at which the subject has data from a scheduled visit present, or if no analyses are planned for the assessment at the mapped visit, the data collected at the early termination or unscheduled visit will be presented in listings only.

In the event of multiple values from unscheduled or early termination assessments within an analysis window, the value closest to the scheduled visit target study day will be used for analyses. If two values tie as closest to the time point (for example, one value is before and the other value is after the time point), then the later value will be selected.

Data collected at all visits will be included in the data listings with visit presented as reported by the site.

6.1.4 Adjustments for Covariates

Not applicable to this study.

6.1.5 Handling of Dropouts or Missing Data

If a partial date is reported where the day is missing, then the day will be imputed as the first day of the month unless the month is the same month as the first injection then the day will be that of first injection with the month and year remaining the same. If a partial date is reported where the month is missing, then the month will be imputed to January unless the year is the same year as the first injection then the month will be that of first injection with the year remaining the same. If a partial date where both the day and month is missing, follow details as stated previously.

Missing adverse event dates will be imputed using partial date imputation rules as previously described in this Section. Missing data for other parameters will not be imputed for analysis unless otherwise defined.

The primary method for handling missing data for the analysis of the primary and secondary endpoints will be LOCF.

6.1.6 Interim Analyses and Data Monitoring

There is no formal interim analysis planned.

The primary analysis will take place once all Week 24 data have been entered, cleaned and evaluability has been finalized.

To meet the trial's ethical responsibility to its subjects, results will be monitored by a Data Safety Monitoring Board (DSMB) that has no formal involvement with the subjects or the investigation. The 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. To minimize risk, cumulative safety data will be reviewed by the DSMB. Principal investigators (PIs), additional 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 are 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.

6.1.7 Multicenter Studies

The clinical study will be conducted under a common protocol for each investigational site with the intention of pooling the data for analysis. Every effort will be made to promote consistency in study execution at each investigational site. Primarily because of the small sample size of the trial, analyses will not formally test for any difference between effects by center.

6.1.8 Multiple Comparisons/Multiplicity

No multiplicity adjustments will be implemented due to exploratory nature of comparisons.

6.1.9 Use of an Efficacy Subset of Subjects

No efficacy subsets will be summarized.

6.1.10 Active-Control Studies Intended to Show Equivalence

Not applicable to this study.

6.1.11 Examination of Subgroups

Not applicable to this study.

6.2 Disposition of Subjects

The number of subjects included in each analysis population (randomized, FAS, safety) will be summarized. The number of subjects randomized, completed, and discontinued (including the

reasons for discontinuation) will be summarized. The number of randomized wounds per subject will also be summarized.

Subjects who are excluded from an analysis population will be summarized by the reasons for exclusion.

6.3 Protocol Deviations

Protocol deviations will be evaluated as per the clinical database and additionally tracked by operational study team members. Protocol deviations will be summarized according to category and a by-subject listing of all protocol deviations will be presented.

6.4 Data Sets Analyzed

Subjects will be summarized based on the primary reason for exclusion.

6.4.1 Randomized Population

All subjects who are randomized to study treatment will be included in the randomized population. Listings and summaries will be provided for all randomized subjects.

6.4.2 Full Analysis Set (FAS)

All subjects in the randomized population who are administered FCX-007 will be included in the FAS. The primary efficacy analysis will be performed using the FAS.

In the case that a Standard of Care (SOC) wound is inadvertently injected with FCX-007, then the primary efficacy analysis will consider this wound in the SOC group (as randomized) as per the intent-to-treat philosophy.

If any treated wounds from the second or third pairs are not able to be fully treated for any reason, then these wounds will not be included in efficacy analyses beyond the timepoint they were not able to be treated, i.e., Day 1 or Week 12.

6.4.3 Safety Population

The safety population is defined as all subjects who were administered FCX-007. All safety analyses will be performed using the safety population.

6.5 Demographic and Other Baseline Characteristics

All baseline summaries will be done on the FAS and safety populations.

Sex, race, and ethnicity will be summarized by counts and percentages. Age, height (in), and weight (lbs.) will be summarized with descriptive statistics. Also, disease measures such as

mutation, baseline COL7 IF and EM characteristics if applicable, and antibody presence will be summarized.

Genetic testing results will be presented in listings. Vital signs collected at screening will be summarized with descriptive statistics.

Medical histories will be coded using the MedDRA dictionary and presented in a by-subject listing.

6.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded to preferred name and Anatomical Therapeutic Chemical (ATC) classification of ingredients using the World Health Organization (WHO) Drug dictionary (WHO-DDE). Counts and percentages will be provided to summarize the use of medications reported throughout the study. The number and percent of subjects who took medications will be shown by ATC level 2 term and preferred name. Medications which start prior to first injection will be considered prior medications. Ongoing medications and medications ending after the date of first injection will be considered concomitant medications. Medications which are both prior and concomitant will be included in summary. Incomplete start and end dates which could be either prior to first injection or after first injection will be considered prior to first injection.

A by-subject listing of all prior and concomitant medications will be presented.

6.7 Analysis of Efficacy

6.7.1 Primary Efficacy 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 number and percentage of complete closures will be reported by treatment group.

The primary efficacy analysis will be presented for the FAS population.

6.7.2 Secondary Efficacy Analysis

For all secondary endpoints, numbers and percentages of complete closures will be reported by treatment group.

The secondary efficacy analysis will be presented for the FAS population.

6.7.3 Supportive Efficacy Analysis

Durability of wound closure from Week 24 through Week 48 is defined as a wound assessed as closed at Week 24 (with confirmatory closure at Week 22), as well as closed at the Week 36 and Week 48 WA. Summaries will be done for both First wounds and all qualifying wounds (those assessed as closed at Week 24) by treatment group.

Durability of wound closure from Week 24 through Week 36 is defined as a wound assessed as closed at Week 24 (with confirmatory closure from Week 22), as well as closed at the Week 36 WA. Summaries will be done for both First wounds and all qualifying wounds (those assessed as closed at Week 24) by treatment group.

Durability of wound closure from Week 12 through Week 48 is defined as a wound assessed as closed at Week 12, as well as closed at Weeks 24 (with confirmatory closure at Week 22), 36 and 48 WAs. Summaries will be done for both First wounds and all qualifying wounds (those assessed as closed at Week 12) by treatment group.

Durability of wound closure from Week 12 through Week 36 is defined as a wound assessed as closed at Week 12, as well as closed at Weeks 24 (with confirmatory closure at Week 22) and 36 WAs. Summaries will be done for both First wounds and all qualifying wounds (those assessed as closed at Week 12) by treatment group.

The Wong-Baker FACES Pain Rating Scale will be summarized by visit with changes from Baseline at Weeks 12, 24, 36 and 48. Summaries will be done for the First wound pair, and all wound pairs, as well as by maximum across wounds (treated and control).

COL7 expression in treated wounds as assessed by IEM and IF at Weeks 36 and 48 will be presented in listings.

6.7.4 Other Efficacy Analysis

Digital imaging data will be presented in data listings.

6.7.5 Sensitivity Analyses

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

In the event of missing Week 24 WAs (with confirmatory closure at Week 22) for either wound, sensitivity analyses will consider these wounds as failures.

6.8 Safety Evaluation

6.8.1 Extent of Exposure

For randomized subjects, findings from the treated wounds will be summarized. These include the total cell exposure, number of treated wounds, number of injection sessions, baseline surface area of the wound, and timing of re- administrations, whether wound was completely or partially treated, number of injections per wound, and other relevant information collected on the CRF.

6.8.2 Adverse Events

All AEs that occur during the study will be recorded and classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology. Treatment-emergent AEs (TEAEs) are defined as AEs with an onset on or after the date of the first injection. Adverse events noted prior to the first injection that worsen after baseline will also be reported as AEs and included in the summaries.

Treatment-emergent AEs will be summarized by the number of subjects reporting a TEAE, system organ class, preferred name, severity, relationship to FCX-007 (causality), whether within treatment area, and seriousness. When summarizing AEs by severity and relationship, each subject will be counted once within a system organ class or a preferred term by using the event with the highest severity and greatest relationship within each classification.

Serious AEs (SAEs) will be summarized by severity and relationship to investigational product, and individual SAEs will be listed by subject. In addition, a list of subjects who prematurely discontinue from the study due to an AE will be provided.

Listings will be presented for all adverse events as well as for serious adverse events, and adverse events leading to discontinuation from the study.

6.8.3 Clinical Laboratory Evaluation

Local laboratory tests include bacterial wound cultures, urine pregnancy tests, HIV, Hep B, and Hep C, as well as hematology and chemistry. Outside laboratory testing includes genetic testing, RCL analysis and COL7 antibody assays.

Bacterial wound cultures, urine pregnancy tests, HIV, Hep B, Hep C, and genetic testing results will be presented in listings. Hematology and chemistry results will be summarized by visit, presented in listings and presented as shift tables. RCL analysis and COL7 antibody assays will be summarized by visit and presented in listings.

6.8.4 Other Observations Related to Safety

6.8.4.1 Vital Signs

Vital signs will be presented by visit as observed values and changes from Baseline using descriptive statistics.

6.8.4.2 Physical and Skin Examinations

Physical and skin examination data will be presented in a by-subject listing.

6.8.4.3 Skin Biopsies

If skin biopsies are performed, results will be presented in listings.

7. DETERMINATION OF SAMPLE SIZE

The originally planned sample size was 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 would have provided 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.

However, due to limitations in manufacturing lentiviral vector required for manufacturing FCX-007, the sample size was limited to 6 enrolled subjects.

8. CHANGES IN THE PLANNED ANALYSES

Due to changes in sample size, originally planned formal analyses of primary and secondary endpoints analyses are now descriptive. In addition, the Per-Protocol population and associated analyses have been removed.

9. REFERENCES

1. Rashidghamat E, McGrath JA. Novel and emerging therapies in the treatment of recessive dystrophic epidermolysis bullosa. Intractable Rare Dis Res. 2017 Feb;6(1):6-20.

2. Fritsch A et al. A hypomorphic mouse model of dystrophic epidermolysis bullosa reveals mechanisms of disease and response to fibroblast therapy. J Clin Invest. 2008 May;118(5):1669-79.

3. RAC (Recombinant DNA Advisory Committee) Minutes of Meeting and webcast, March 14, 2007, Available at http://osp.od.nih.gov/sites/default/files/RAC_minutes_03-07.pdf. Accessed March 11, 2014.

4. Lazarus GS et al. Definitions and guidelines for assessment of wounds and evaluation of healing. Arch Dermatol. 1994 Apr;130(4):489-93.

5. Cianfarani F et al. Pathomechanisms of Altered Wound Healing in Recessive Dystrophic Epidermolysis Bullosa. Am J Pathol. 2017 Jul;187(7):1445-1453.

6. Solis D et al. Poster 219 Natural history of chronic wounds in patients with recessive dystrophic epidermolysis bullosa. SID Meeting 2017 https://www.jidonline.org/article/S0022-202X(17)30416-5/fulltext

7. Adni T et al. The psychosocial impact of chronic wounds on patients with severe epidermolysis bullosa. J Wound Care. 2012 Nov;21(11):528, 530-6, 538.

8. FDA Human Gene Therapy for Rare Diseases Guidance for Industry, January 2020. https://www.fda.gov/media/113807/download

9. Fine JD et al. Assessment of mobility, activities and pain in different subtypes of epidermolysis bullosa. Clin Exp Dermatol. 2004 Mar;29(2):122-7.

10. Goldschneider KR et al. Pain care for patients with epidermolysis bullosa: best care practice guidelines. BMC Med. 2014 Oct 9;12:178.