The treatment of wounds associated with recessive dystrophic epidermolysis bullosa with local injections of gene-corrected, collagen VII-expressing autologous human dermal fibroblasts

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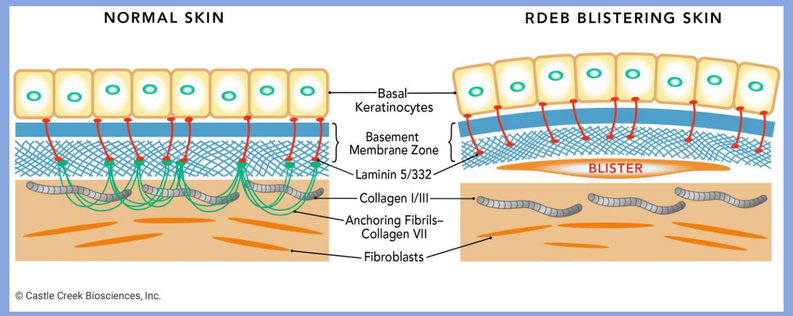
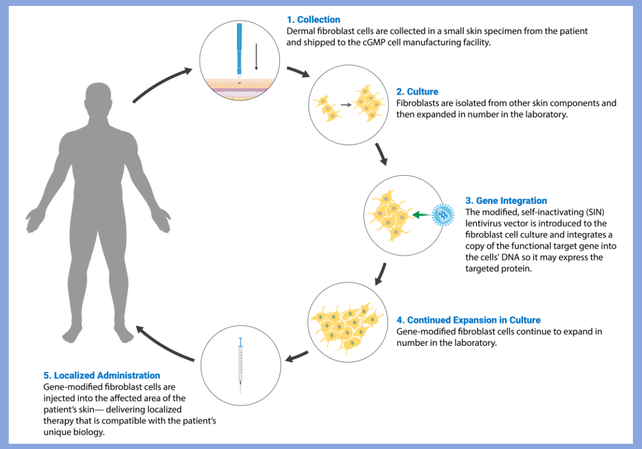
INTRODUCTION and BACKGROUND

Recessive dystrophic epidermolysis bullosa (RDEB) is caused by mutations in the COL7A1 gene encoding type VII collagen (COL7).



There are no curative treatments for RDEB; therapy is limited to palliative wound care. This Phase 1/2 clinical study (NCT02810951) assessed the safety and preliminary effectiveness of the injection of genetically-corrected COL7 expressing autologous human fibroblasts (FCX-007*) to chronic RDEB wounds.

COL7A1 GENE-CORRECTED AUTOLOGOUS FIBROBLASTS: PRODUCTION OF FCX-007



STUDY OVERVIEW and BASELINE CHARACTERISTICS

Six subjects with severe generalized RDEB (9-38 years of age) with various COL7A1 mutations resulting in undetectable COL7 expression and a lack of intact anchoring fibrils (AF) enrolled in this clinical study.

Autologous fibroblasts were isolated from their respective skin biopsies, transduced with a third-generation self-inactivating lentiviral vector encoding the wild type COL7A1 gene, and expanded for local injection. Eligible treatment wounds (4.3 cm^2 to 34.1 cm^2) were chronically present prior to intradermal injection with FCX-007; a comparator wound was not treated. Wounds were excluded if there was evidence of infection, or if located on mucous membranes, face, of hands and feet. Four of the six subjects received a second treatment 4 to 52 weeks after the initial injection; all were to be followed through 52 weeks. The wounds were assessed for efficacy, including complete wound healing (defined as ≥90%), and for evidence of effect by IF and IEM.

ID/Age/Sex	0101/26/M	0102/21/M	0103/33/M	0104/38/F	0105/33/M	0106/9/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 (by IF/WB)	Negative/ NC-1 positive	Negative/ NC-1 positive	Negative/ NC-1 positive	Negative/ NC-1 negative	Negative/ NC-1 positive	Negative/ 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

RESULTS: SAFETY

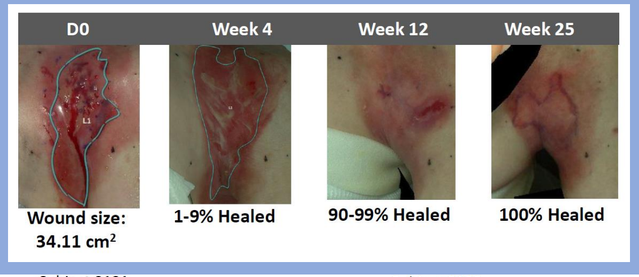
FCX-007 was generally safe and well tolerated up to 52 weeks post-administration with no COL7-antibody or replication competent lentivirus (RCL) detected. There were no serious adverse reactions reported. Short-lived injection site erythema and discoloration were evaluated to be related, nonserious events.

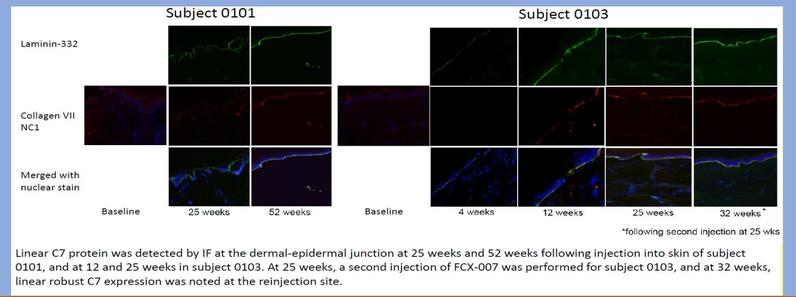
RESULTS: EFFECTIVENESS

At 12 weeks, 80% (8/10) of treated wounds demonstrated complete wound healing, compared to 0% of the untreated control wounds. Linear COL7 expression at the dermal-epidermal junction and restoration of AF was confirmed in treated sites.

Wound Closure %	≥50%	≥75%	Complete
FCX-007 Treated Wounds	90% (9/10)	80% (8/10)	80% (8/10)
Untreated Control Wounds	44% (4/9)	11% (1/9)	0% (0/9)

FCX-007 Treated Wound (Subject 0106):





Linear C7 protein was detected by IF at the dermal-epidermal junction at 25 weeks and 52 weeks following injection into skin of subject 0101, and at 12 and 25 weeks in subject 0103. At 25 weeks, a second injection of FCX-007 was performed for subject 0103, and at 32 weeks, linear robust C7 expression was noted at the reinjection site.

CONCLUSION

The local injection of gene-corrected autologous fibroblasts expressing COL7 (FCX-007) to the wounds of RDEB appears to be generally safe, and complete wound healing is typically exhibited. The durability of wound healing will be evaluated over a longer period of time in a Phase 3 clinical study (NCT04213261).

*FCX-007 is also known as D-Fi.

This study is supported by Castle Creek Biosciences.

The authors are grateful to each of the patients who participated in this clinical study.