Pre-Clinical Development of a Genetically-Modified Human Dermal Fibroblast (FCX-007) for the Treatment of Recessive Dystrophic Epidermolysis Bullosa

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ABSTRACT AND INTRODUCTION

Recessive dystrophic epidermolysis bullosa (RDEB) is an autosomal recessive, inherited skin disease caused by null mutations within the type VII collagen gene (COL7A1). The mutations cause an absence or reduction of functional collagen VII, which make up anchoring fibrils that maintain binding of the epidermis to the dermis (Figure 1). The disease is characterized by a mechanical fragility and repeated blister formation in the sub-lamina dema, at the level of the structurally defective anchoring fibrils. Currently, there is no effective therapy for this disease, and death usually is the result of aggressive squamous cell carcinoma, sepsis, or malnutrition.

We are developing an autologous, genetically-modified fibroblast cell therapy that is anticipated to improve skin function in RDEB patients through restoration of collagen levels. A patient's fibroblasts will be harvested, genetically modified ex-vivo with a functional COL7A1 gene, and expanded in culture (GM-HDF-COL7A1 or FCX-007) (Figure 2). Fu ex vivo transduction will occur through the use of a replication-defective, self-replicating (SN) lentiviral vector. After expansion, the fibroblasts are administered back to the patient as a local intradermal injection into target wound margins. The resulting increase in anchoring fibrils is anticipated to stabilize the connection between skin layers and reduce blistering tendency.

In vitro product development data indicates that cGMP scale GM-HDF-COL7 cells express full-length type VII collagen exhibiting the proper trimeric structure, size, and binding functionality (Figures 3, 4). We present results from a pre-clinical animal model evaluating FCX-007 in RDEB and normal human skin xenografts implanted into immunodeficient SCID mice (Figure 5). The goals of the study are to confirm persistence, distribution and localization of COL7, and to evaluate any potential for product toxicity or vector biodistribution (Table 3).

We also present the study design for a proposed Phase I/II clinical trial to treat RDEB patients with FCX-007 (Table 2). The primary endpoints for the study are to evaluate safety and to confirm the formation of anchoring fibrils at the basement membrane zone (BMZ) in biopsies collected from subjects after product administration.

RESULTS


B. General structure of normal and RDEB skin. COL7 anchoring fibrils bind to other collagen extracellular matrix proteins, and are involved in the mechanical failure of the dermis to the epidermis. Absence of anchoring fibrils can lead to blister formation.

Figure 3

A. Knockout COL7 expression in human skin.

B. COL7a1 transduction improves epidermal attachment.

C. Transduction improves epidermal attachment.

D. COL7a1 transduction improves epidermal attachment.

Table 1: Toxicology/BioDistribution Results Summary

<table>
<thead>
<tr>
<th>Study Design for Phase I/II Clinical Trial</th>
<th>Statement of Purpose</th>
<th>Objective</th>
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<td>Phase I/II FCX-007 (Genetically Modified Autologous Human Dermal Fibroblasts) for Recurrent Dystrophic Epidermolysis Bullosa (RDEB)</td>
<td>1) To evaluate the safety of FCX-007 2) To evaluate COL7 expression and the presence of anchoring fibrils resulting from FCX-007 3) To analyze wound healing as a result of FCX-007 administration</td>
<td>1) The primary objective of this protocol is to establish the safety of FCX-007 2) To evaluate mechanism of action of FCX-007 at weeks 4, 12, 24, 52, and 72 weeks and at any point of time or any other point where adverse events may develop up to 96 weeks 3) To evaluate the efficacy of FCX-007 through an intra-subject, paired analysis of the target wound area at weeks 4, 12, 24, 52, and 72 weeks and at any point of time or any other point where adverse events may develop up to 96 weeks 4) To evaluate the incidence and severity of adverse events 5) To evaluate any post-marketing adverse events 6) To evaluate any post-marketing adverse events</td>
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