A Pivotal Phase III Trial of COL7A1 Gene-Corrected Autologous Fibroblasts (D-Fi) for Dystrophic Epidermolysis Bullosa

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OBJECTIVE

- To design a registrational trial to establish the wound healing effect of dabocemagene autoficel (D-Fi) in patients with dystrophic epidermolysis bullosa (DEB) and to further delineate the safety profile of this cellular gene therapy delivered by intradermal injection.

BACKGROUND

- Epidermolysis bullosa (EB) is a clinically and genetically heterogeneous group of inherited blistering diseases that affect the skin and mucosal membranes. The 4 main types are EB simplex, junctional EB, dystrophic EB, and Kindler syndrome; these can be further subtyped. Globally, EB affects approximately 500,000 people,[1] with approximately 25% of affected individuals having DEB.[2]
- Two major types of DEB are described based on the autosomal inheritance pattern: recessive DEB (RDEB) and dominant DEB (DDEB); each of these is further divided into multiple subtypes. All DEB subtypes are caused by mutations in the type 7 collagen gene (COL7A1), which codes for the alpha-1 chain of type 7 collagen protein (COL7). The mutations cause an absence or reduction of functional COL7, the primary component of anchoring fibrils (AF) in the basement membrane zone between the dermis and the epidermis. Absent or reduced AF function causes epidermal-dermal separation 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.
- RDEB is associated with significant morbidity due to chronic and recurrent blistering and subsequent scarring on skin surfaces and mucosal membranes that substantially negatively impact day-to-day functioning. The mortality rate for patients with RDEB is nearly 10% by 10 years of age, almost 40% by 20 years of age, and 72% by 30 years of age. Mortality is usually the result of aggressive squamous cell carcinoma (SCC), sepsis, or malnutrition (due to an inability/unwillingness to eat because of mouth/esophageal involvement).[3] Like RDEB, DDEB may be associated with blistering at birth or soon thereafter. In many DDEB-affected patients, some AFs are functionally intact resulting in a milder phenotype or clinical presentation than typically observed in those with RDEB. Morbidity may be substantial for these patients due to persistent and recurrent blistering and subsequent scarring on skin surface.
- There is no curative treatment for RDEB or DDEB. Optimal supportive treatment of the cutaneous and mucosal DEB lesions includes a combination of protective therapies and dressings, and treatment of wounds, including with a recently approved topical cellular gene therapy, and associated complications (eg, localized infection).
- D-Fi (FCX-007; Castle Creek Biosciences) is an intradermally administered product comprised of autologous fibroblasts isolated from a patient's own skin biopsies and then transduced with a lentiviral vector containing the full-length COL7A1 gene to produce functional COL7. The safety and efficacy of D-Fi is being studied for the treatment of wounds in patients with DEB without regard to specific mutation, based on the certain paucity of functional COL7 in affected patients.

RATIONALE

- D-Fi has been investigated in a Phase 1/2 study (FI-EB-001; NCT 02810951) and a Phase 3 study (FI-EB-002; NCT 04213261) that was terminated early due to the unavailability of vector to deliver the modified COL7A1 gene. Each trial enrolled 6 patients with completion through the 48-week treatment period, and patients from each study remained in a long-term follow-up period in the Phase 3 study. In the primary wound pair of each patient, complete 100% wound closure was achieved in 67% of D-Fi treated wounds versus 0% of control wounds in the completed Phase 1/2 study and in 17% of D-Fi treated wounds versus 0% of control wounds in the terminated Phase 3 study. D-Fi was generally well tolerated with no treatment-related systemic adverse events (AEs); injection-site AEs in the 12 patients included 2 reports of pain and 1 report each of discoloration, erythema, hemorrhage, and swelling. No replication-competent lentivirus or COL7 antibody responses were observed.[4]
- The US Food and Drug Administration guidance on Human Gene Therapy for Rare Diseases suggests that an intra-subject control approach, which is feasible in some rare skin diseases, may be a useful trial design.[5] This study is designed in accordance with this approach (**Figures 1 and 2**): each patient has an assigned target wound pair; one of the wounds in this pair will be randomly assigned as the target treatment wound (D-Fi administered), and the other wound as the control wound (standard of care with no treatment administered). The matched control wound will be untreated since multiple placebo injections may cause wound instability and increased pain. A blinded clinical assessor will determine if the target wounds are open or closed at each assessment.

METHODS

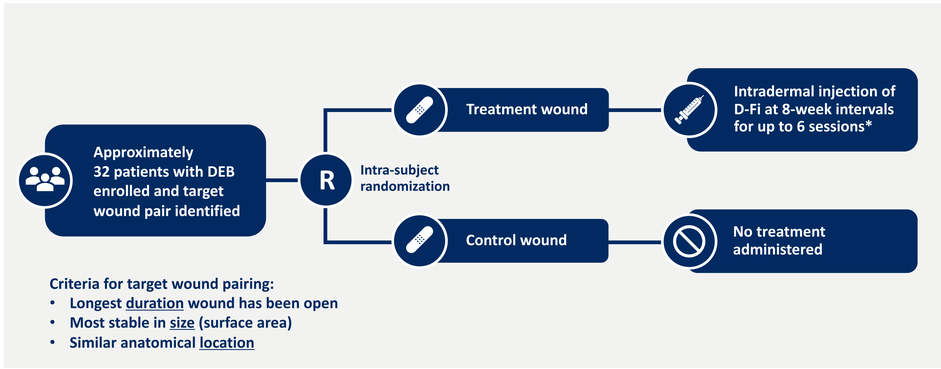
INCLUSION CRITERIA

- Male or female ≥18 months of age at screening
- Clinical diagnosis of DEB with COL7A1 genetic mutation
- Presence of ≥2 persistent, non-healing or recurrent wounds for ≥4 weeks prior to Day 1

EXCLUSION CRITERIA

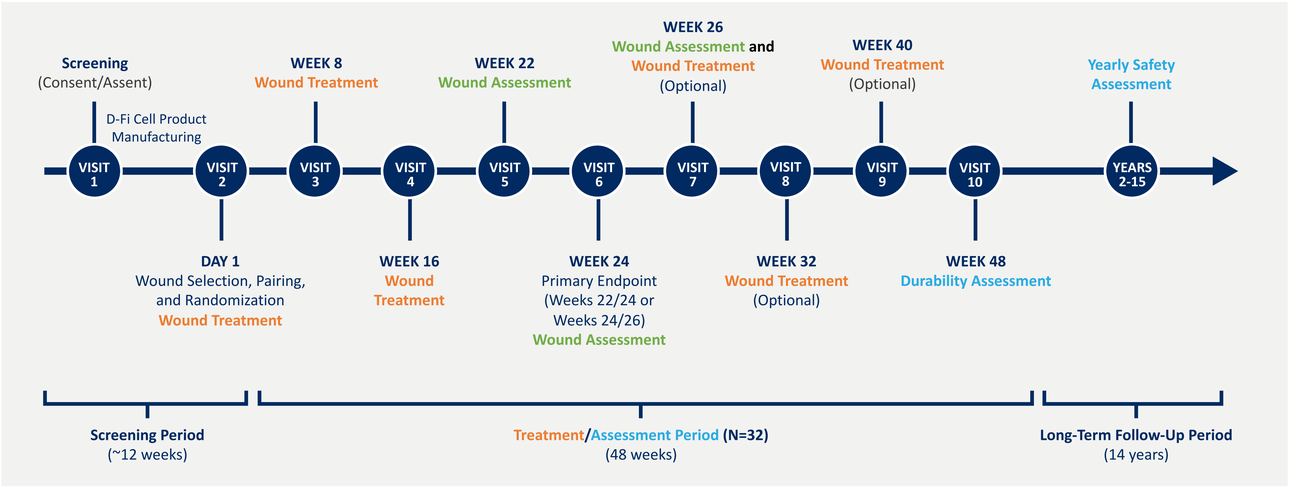
- Clinically significant abnormalities on exam or lab results; significant comorbid conditions, including diabetes mellitus, renal failure, thrombocytopenia, and unstable anemia
- History of malignancy within the previous 2 years (exceptions: basal cell carcinoma or cutaneous SCC that has been treated with no evidence of recurrence or metastasis)
- Female who is pregnant or breast feeding
- Active alcohol or drug addiction
- Hypersensitivity to planned anesthesia medication
- Presence of COL7 antibodies

FIGURE 1. STUDY DESIGN



*The treatment wound will be injected at Day 1 (Visit 2) and Weeks 8 (Visit 3), 16 (Visit 4), and 24 (Visit 6). The primary efficacy endpoint will be evaluated at Weeks 22 and 24 or Weeks 24 and 26. Subsequently, additional treatment sessions may occur at Weeks 26 (Visit 7), 32 (Visit 8), and 40 (Visit 9). At these visits, unclosed and/or re-opened treatment and control wounds may be treated with D-Fi. Additional DEB wounds ≥6 inches (15 cm) from the target wound pair may also be treated at the discretion of the investigator.
DEB = dystrophic epidermolysis bullosa; D-Fi = dabocemagene autoficel.

FIGURE 2. STUDY SCHEMATIC



D-Fi = dabocemagene autoficel.

OUTCOMES

PRIMARY EFFICACY OUTCOME

- Complete (100%) wound closure of the target wound pair at either Weeks 22 (Visit 5) and 24 (Visit 6) or at Weeks 24 (Visit 6) and 26 (Visit 7), as determined by a blinded clinical assessor

SECONDARY EFFICACY OUTCOMES

- Complete (100%) wound closure of the target wound pair at visits earlier than Week 24 as determined by a blinded clinical assessor
- Durability of wound closure post-Week 24 through Week 48 as determined by a blinded clinical assessor
- Change from baseline in the Wong-Baker FACES Pain Rating Scale in the target wound pair at all visits
- Partial wound closure (categorical) of the target wound pair at all visits, as determined by a blinded clinical assessor

SAFETY OUTCOMES

- Evaluation of treatment-emergent AEs
- Physical and skin examinations
- Vital signs
- Laboratory assessments (hematology and chemistry tests)
- Presence of replication-competent lentivirus
- Antibody response to COL7

STATISTICAL METHODOLOGY

- Each patient will serve as their own control, as the target wound pair will be randomly assigned as the treatment wound (D-Fi administered) or control wound (no treatment administered). Statistical analyses will be performed using 2-sided tests at a Type I error rate of 0.05. Primary, secondary, and exploratory endpoints will be tested using a rank order hierarchy to preserve alpha.
- Based on data from a completed Phase 1/2 study and a terminated Phase 3 study, complete 100% wound closure is assumed for 60% of treatment wounds and 15% of control wounds. A sample size of 32 patients provides approximately 85% power at a significance level of 0.05 to detect a difference of 45% between the treatment wounds and the control wounds when there are 70% discordant pairs, using a McNemar's test, and numerical enumeration method for calculating power.

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DISCLOSURES TMC is an employee of Paragon Biosciences, LLC, a company that founded Castle Creek Biosciences, LLC. MS is a former employee and is currently consultant for Castle Creek Biosciences, LLC. KH and RB are employees of Castle Creek Biosciences, LLC. Technical editorial assistance was provided by Synchrony Medical Communications, LLC, West Chester, PA. Funding for this assistance was provided by Castle Creek Biosciences, LLC.