Interim update from a Phase 1/2 trial examining the safety and tolerability of PTR-01, a collagen 7 protein replacement therapy, in patients with recessive dystrophic epidermolysis bullosa

Anna L. Bruckner[1], Jean Tang[2], Mei Chen[3], David T. Woodley[3], Douglas Keene[4], Kathleen Peoples[1], Emily Gorell[2], Melissa Barriga[2], Hal Landy[5], Ramsey Johnson[5], Deborah Ramsdell[5]

[1]University of Colorado School of Medicine and Colorado Children's Hospital, Aurora, Colorado, USA
[2]Department of Dermatology, Stanford University School of Medicine, Redwood City, California, USA
[3]Department of Dermatology, The Keck School of Medicine, University of Southern California, Los Angeles, California, USA
[4]Shriner's Hospital for Children, Portland, Oregon, USA
[5]Phoenix Tissue Repair Inc., Boston, Massachusetts, USA

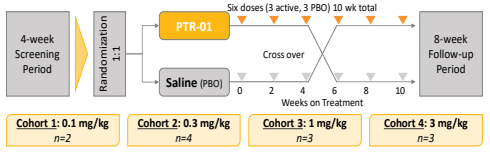
Background

- Dystrophic epidermolysis bullosa (DEB) is a rare genodermatosis due to mutations in the *COL7A1* gene encoding the α-chain of collagen 7 (C7). C7 deficiency results in dermal-epidermal junction (DEJ) separation with severe, painful blistering and scarring. Dominant (DDEB) and recessive (RDEB) forms occur. RDEB is typically more severe with wounds affecting not just skin but all mucosal membranes. Oral ulcers cause fusion of the tongue to the mouth floor and progressive microstomia. Esophageal erosions cause strictures and severe dysphagia requiring periodic dilatation. Nutritional deficiency and anemia are common. Corneal erosions can lead to scarring and loss of vision. Blistering and scarring of the hands and feet result in a characteristic pseudosyndactyly. The lifetime risk of aggressive squamous cell carcinoma is >90%.(1)
- The treatment of DEB is mainly palliative and none of the therapeutics currently in development address its systemic nature. PTR-01 is a recombinant human C7 given intravenously as replacement therapy. In mouse models of DEB, PTR-01 distributed to the DEJ, corrected dermal-epidermal separation and in mice, prolonged survival.(2) We describe interim results from a first-in-man study of PTR-01 in the treatment of adults with RDEB.

Methods

- Phase 1/2 randomized, double-blind, placebo-controlled, multiple dose, dose escalation, cross-over study in adults with genetically & histologically confirmed RDEB.
- Eligible patients are randomized to either PTR-01 or placebo in 4 dosing cohorts and receive 3 IV infusions at 2 week intervals. After a 2-week washout, the patient crosses over to the other treatment and receives 3 additional IV infusions. The patient is then observed for an additional 8 weeks.
- Dose and number of patients in each cohort are summarized in Figure 1, below.
- Primary endpoint of this first-in-man study of PTR-01 is safety, as measured by adverse events, infusion-associated reactions and immunogenicity.
- Secondary endpoints include pharmacokinetics (PK), deposition of PTR-01 at the dermal-epidermal junction (DEJ) by immunofluorescence and formation of anchoring fibrils by electron microscopy.
- Exploratory endpoints include suction blister time, wound healing, assessments of itch, pain and quality of life and nutritional markers.

Figure 1: Design of Study PTR-01-001



Results

Primary Outcome: Safety

- All 9 patients in Cohorts 1 – 3 completed dosing
- 36 treatment emergent AEs
  - No unexpected AEs
  - No serious AEs related to study drug based upon data as of 9 June 2020
  - 20 Not related, 6 Unlikely, 7 Possibly, 3 Probably
  - 22 Mild in severity, 6 Moderate (none related), 8 Severe (not related or unlikely related)
- 3 patients (2 in Cohort 2 and one in Cohort 3) developed low-titers of anti-drug antibodies which have declined over time
- 2 patients in Cohort 3 had mild infusion-associated reactions (IARs) characterized by flushing and mild increase in temperature
  - Events were brief and resolved spontaneously
  - Neither required dose adjustment, slowing of infusion or any other intervention
  - One had low levels of anti-drug antibodies which declined; the other has been negative

Secondary Outcomes: Pharmacokinetics (PK) and C7 in Tissue

Figure 2: PTR-01 Pharmacokinetics by Cohort

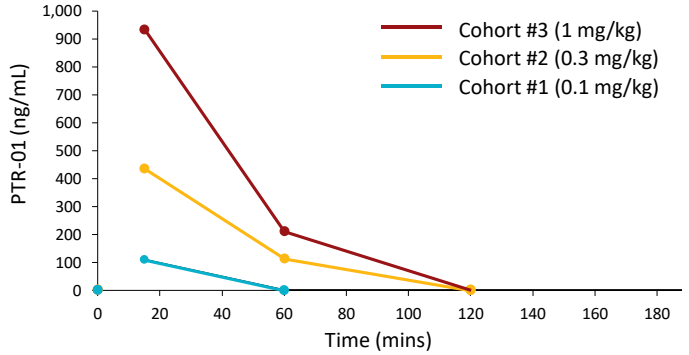


Figure 2. Serum PK shows linear dose response. Of note, only Cohort 3 (1 mg/kg) approaches the levels seen at the minimum effective dose in animal pharmacology studies.

Figure 3: C7 in Tissue by Direct Immunofluorescence: Cohort 3

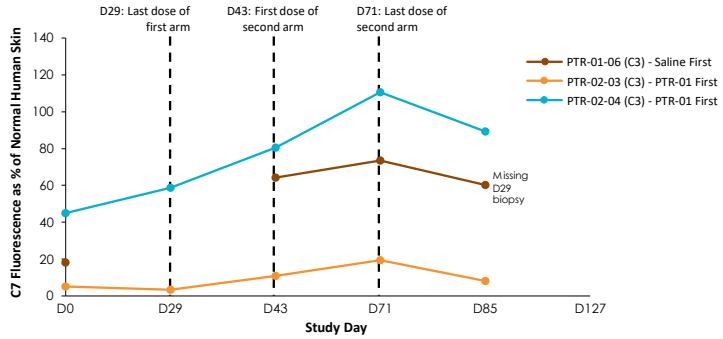


Figure 3. All 3 patients in Cohort 3 showed a 2 – 3 fold increase in C7 immunofluorescence following infusions of PTR-01.

Figure 4: C7 immunofluorescence in Cohort 3 patients

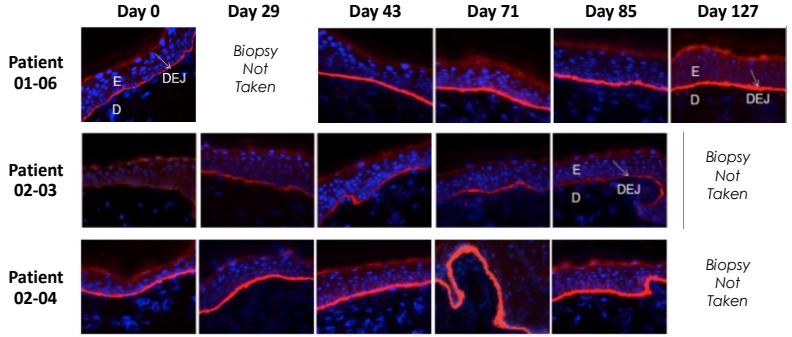


Figure 4. Immunofluorescence staining for C7 in patients in Cohort 3 showed increased C7 at the DEJ in unwounded skin after 3 infusions of PTR-01. Electron microscopy for anchoring fibrils did not show a change from Baseline at these timepoints. White arrow points to enhanced DEJ staining of C7 (average of 200% increase from baseline). We had limited AF data due to few intact biopsies.

Summary and Conclusions

In this short-term, first-in-man study, intravenous PTR-01 was safe and well-tolerated at doses up to 1 mg/kg. At the highest dose studied to date (1 mg/kg), an average increase in tissue C7 by immunofluorescence was noted. Modest positive trends were noted in pharmacodynamic markers, tissue C7 content. Modest positive trends were noted in a pharmacodynamic marker, patient reported outcomes and wound healing. PK data, interpreted in the context of previous animal data, suggest the need for a higher dose of PTR-01 which is being investigated in Cohort 4. Longer term studies will be needed to confirm PTR-01's anticipated effects on systemic features of DEB such as esophageal strictures, pseudosyndactyly, corneal abrasions, etc.

References: 1. Fine JD, Johnson LB, Weiner M et al. Epidermolysis bullosa and the risk of life-threatening cancers: the national EB registry experience, 1986–2006. J Am Acad Dermatol 2009; 60:203–11 (2). Hou et al., Intravenously Administered Recombinant Human Type VII Collagen Derived from Chinese Hamster Ovary Cells Reverses the Disease Phenotype in Recessive Dystrophic Epidermolysis Bullosa Mice. J. Investigative Dermatology 2015 135, 3060-3067