Collagen 7 (C7) protein replacement therapy (PTR-01) durably reduced wound size and symptoms in patients with recessive dystrophic epidermolysis bullosa (RDEB)

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INTRODUCTION

Phoenix Tissue Repair (PTR) is developing recombinant human collagen 7 (rC7) as a disease-modifying intravenous (IV) replacement therapy for patients with dystrophic epidermolysis bullosa (DEB). Replacement of the aberrant or missing protein with systemic, IV-administered rC7 is predicted to improve skin and mucosal integrity resulting in durable wound healing and reduction of the cutaneous and systemic complications of DEB. We previously reported results from a first-in-human study of PTR-01 in the treatment of adults with Recessive Dystrophic Epidermolysis Bullosa (RDEB) in which 8 patients received IV infusions of PTR-01. We now report results from a Phase 2 Open-Label Study of PTR-01 in patients 13 years and older with RDEB.

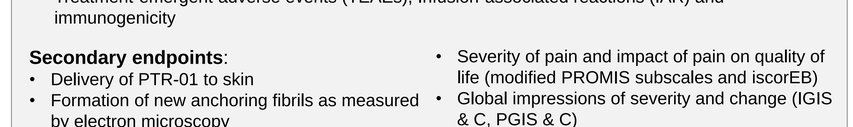
METHODS

Patients ≥ 12 years with a genetic diagnosis of RDEB were enrolled in a Phase 2 open-label study consisting of 3 parts (Figure 1):

- A 4-dose loading period (3.0 mg/kg weekly)
- A 14-week 7-dose maintenance period (3.0 mg/kg every other week) and
- A follow-up period

Main assessments were performed at the end of Parts 1 and 2. In Part 3, patients were followed for 12 weeks and evaluated at the end of Months 1 and 3. Safety was continuously assessed.

Figure 1



Primary endpoints:

- Improvement in a majority of target lesions of at least 2 points using a 7-point Global Impression of Change instrument
- Treatment-emergent adverse events (TEAEs), Infusion-associated reactions (IAR) and immunogenicity

Secondary endpoints:

- Delivery of PTR-01 to skin
- Formation of new anchoring fibrils as measured by electron microscopy
- Wound area of target lesions by imaging
- Investigator Global Impression of Change (IGIC)
- Total body wound surface area
- Severity of pain and impact of pain on quality of life (modified PROMIS subscales and iscorEB)
- Global impressions of severity and change (IGIS & C, PGIS & C)
- Wound care burden
- Patient interviews / anecdotal reports
- Markers of skin fibrosis

RESULTS

Parameter	Overall (N=6)
Number of patients with Day 120 assessment	5
Responders[a] [n (%)]	4 (66.7)
Nonresponders [n (%)]	1 (16.7)
Response Rate (95% CI)	80.0 (28.4, 99.5)
Total wound response[b] for all patients [m/M (%)]	18/26 (69.2)

m = number of wounds that met the response criteria; M = total number of wounds
[a] Responders were patients with a ≥ 2-point increase in the wound-specific 7-point assessment scale in ≥ 50% of their wounds
[b] Total wound response is the total number of wounds (all patients) with a ≥ 2-point increase in the wound-specific 7-point assessment scale for all patients

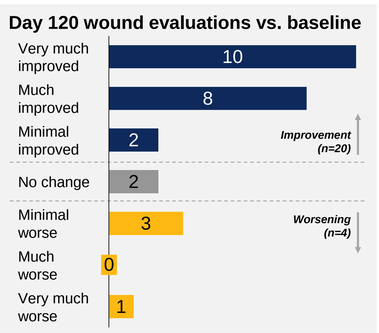
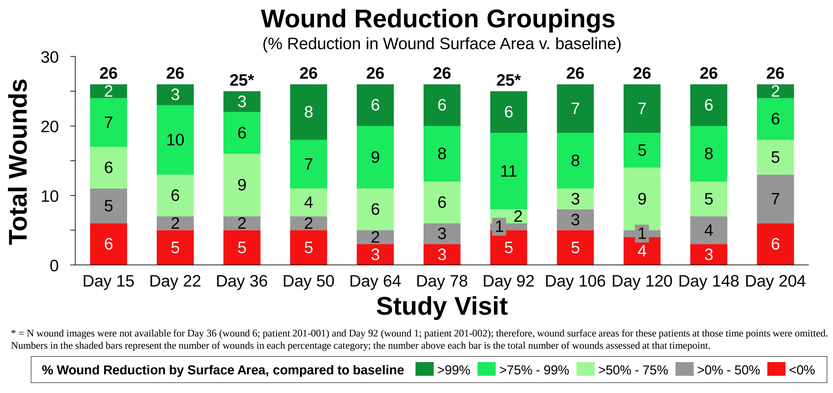


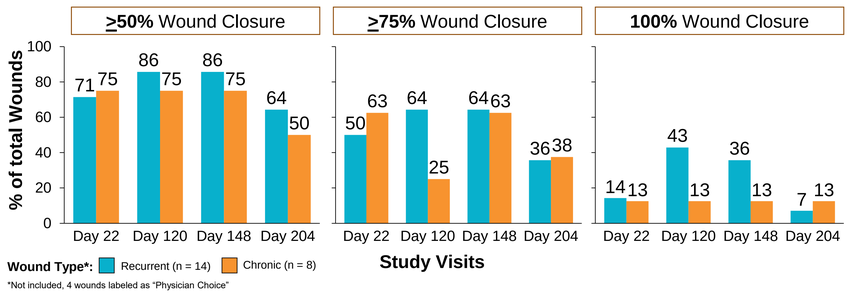
Figure 2: Wound Response on Day 120 compared to Baseline by Wound-Specific 7-Point Scale. Treatment with PTR-01 led to rapid, consistent, and durable wound healing. By day 15, 15 /26 wounds (57.7%) met the response criteria of ≥2-point increase on the wound-specific scale, and at day 120, 18/ 26 wounds (69.2%). Based on these criteria, 4/ 6 patients (66.7%) were responders since they had ≥2-point increase in ≥50% of their wounds at day 120.



* = N wound images were not available for Day 36 (wound 6; patient 201-001) and Day 92 (wound 1; patient 201-002); therefore, wound surface areas for these patients at those time points were omitted. Numbers in the shaded bars represent the number of wounds in each percentage category; the number above each bar is the total number of wounds assessed at that timepoint.

Figure 3: Wound Response By Percent Reduction in Wound Surface Area By Canfield Imaging. Wounds exhibited a rapid response to treatment with a majority (80%) reaching >50% closure by Day 78. At Day 120, the end of treatment over 80% of wounds closed >50% compared to baseline. Durability of treatment lasted one month after the last dose with treatment effects waning starting at Day 204

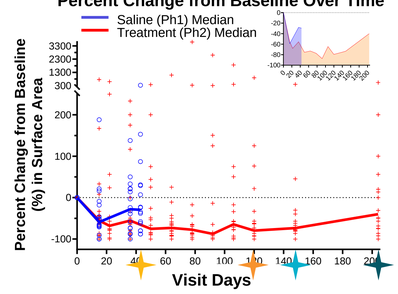
RESULTS



*Not included, 4 wounds labeled as "Physician Choice"

Figure 4: PTR-01 Demonstrated Wound Closure in Both Chronic and Recurrent Wounds. Robust wound healing response was observed across different wounds types: small and large, chronic and recurrent. Majority of wounds achieved healing of > 50 and > 75% on Day 120

a. Phase 1 Placebo and Phase 2 Treated Wounds Percent Change from Baseline Over Time



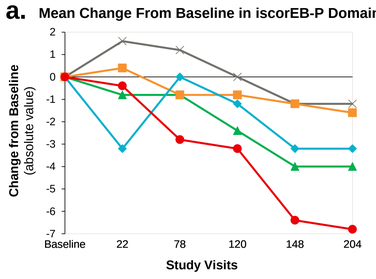
b. Median in AUC of Wound Surface Area over Time compared to Percentage of Baseline

Timepoint	Phase 1 (Placebo) (n=21 wounds)	Phase 2 (PTR-01) (n=26 wounds)
Day 43	75.0%	53.6%*
Day 120	N/A	31.7%
Day 148	N/A	31.0%
Day 204	N/A	37.6%

AUC = area under the curve (cumulative wound surface area from baseline);
N/A = not applicable
* Hodges-Lehmann estimate of difference in medians= -18.01, 95% CI = (-40.35,7.19); Wilcoxon rank-sum p = 0.1776

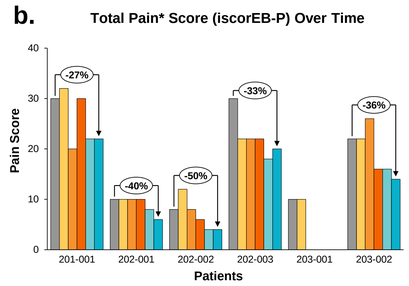
Figure 5: Individual Wound and Median Change from Baseline in Wound Surface Area. Using area under the curve (AUCi) analysis to examine wound size over time relative to baseline, there was greater reduction at day 43 in patients receiving PTR-01 than that observed in a historic Phase 1 PTR-01 study patients receiving placebo (53.6% v. 75%).

a. Mean Change From Baseline in iscorEB-P Domains



iscorEB-P: Patient reported assessment of iscorEB instrument

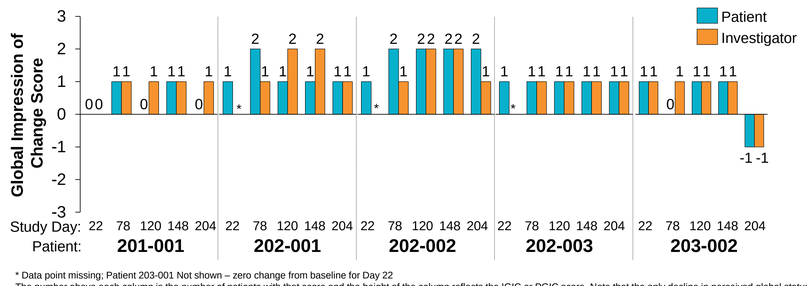
b. Total Pain* Score (iscorEB-P) Over Time



* Total Pain is the sum of the 5 pain subdomains: Overall, Skin, Mouth, Bone & Joint, & Eye Pain

Figure 6: Improvements in Pain, Disease Impact, Activities of Daily Living, Mood and Essential Functions by iscorEB-P [1, 2]. Marked mean and median reductions from baseline to day 204 were observed in iscorEB-Patient scores for pain, essential function, mood, activities of daily living and disease impact

Patient and Investigator Global Impression Score – Change from Baseline

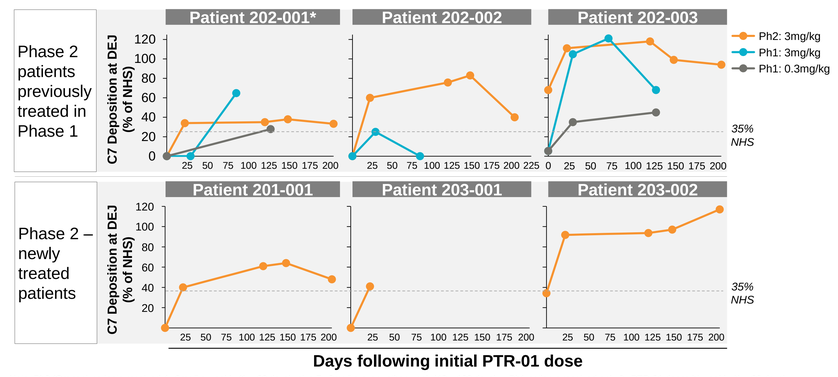


* Data point missing; Patient 203-001 Not shown – zero change from baseline for Day 22
The number above each column is the number of patients with that score and the height of the column reflects the IGIC or PGIC score. Note that the only decline in perceived global status occurred in patient 203-002 at 3 months after the end of treatment.

Figure 7: Investigator and Patient Global Impression of Change (GIC) Score by Patient and Time Point. At days 22, 78, 120, and 148, both IGIC and PGIC scores improved, with good correlation between investigator and patient assessments.

NOTE: PTR-01 is an investigational product and has not been approved by the FDA or any other regulatory authority.

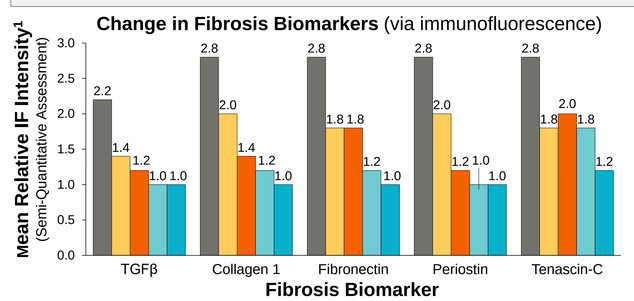
RESULTS



Note: Ph2 (Orange) patients received 4x 3mg/kg weekly (1 – 29 days), plus 7x 3mg/kg every other week (42 – 120 days) v. Ph1 patients received only 3x PTR-01 doses bi-weekly (1 – 29 days); NHS = Normal human skin; * Day 22 and 120 unwounded samples for 202-001 were poor quality, no data – data shown is for wounded sample; Patients 02-06, 02-07, 02-08 participated in the Phase 1/2

Figure 8: Deposition of C7 at the Dermal-Epidermal Junction with PTR-01 Administration. Rapid deposition of rC7 at the DEJ was observed during the loading phase, achieving levels projected to confer a therapeutic effect (35% of normal). These levels were maintained throughout treatment and 1 month following treatment completion.

Change in Fibrosis Biomarkers (via immunofluorescence)



1. Scoring was performed on a 3 pt scale (1=low, 2=moderate, 3=high), N = 5 patients (study completers)

Figure 9: Reduction in Skin Pro-Fibrotic Biomarker Staining with PTR-01 Administration. Biomarkers of fibrosis decreased over the course of treatment from an elevated baseline, and remained reduced after treatment completion.

Figure 9: PTR-01 Was Well Tolerated.

- Twenty AEs were reported for 4 patients, all resolved
- There were no deaths, SAEs, or unexpected AEs
- No AEs led to treatment discontinuation
- All AEs were mild or moderate except a single AE of Anemia, which was considered no- related to study drug
- One patient had infusion reactions that responded to supportive care and resolved within hours
- Three patients had detectable low-titer ADAs, observed at least once during the study. These observations were not associated with clinical or laboratory manifestations
- One patient had high-titer ADAs. This patient had mild infusion reactions and eventually withdrew from the study due to lack of efficacy.

TEAE	# of pts (events)	Grades
Any TEAE	**4 (20)**	**I, II, III**
IARs / AESIs	1 (10)	I
Infections	1 (2)	I
Palpitations	1 (1)	I
Dermatitis	1 (1)	I
Other vitals/lab abnormalities[1]	2 (5)	I, II
Anemia	1 (1)	III

CONCLUSIONS

- Weekly infusions of PTR-01 3.0 mg/kg for 4 weeks followed by every-other-week infusions for 14 weeks were well-tolerated and resulted in:
  - Rapid and sustained improvements in measures of wound healing including;
    - The proportion of patients with at least a 2-point improvement in the majority of their wounds
    - The proportion of total patient wounds with ≥50% reduction in surface area
  - Reduction in several iscorEB domains
  - Deposition of rC7 at the DEJ
  - Reduction of pro-fibrotic biomarkers in the skin
- Investigator and patient global assessments of change were in agreement and reflected improvement in overall disease
- The results of this small study support further investigation of PTR-01 administration for the treatment of DEB.

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[3] Bruckner A.L. et al. "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", SID May 3-8 2021.
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