Assessment of Safety in Repeat Dosing of an In Vivo Topical Gene Therapy for the Treatment of Recessive Dystrophic Epidermolysis Bullosa (RDEB) in a Phase I/II Trial

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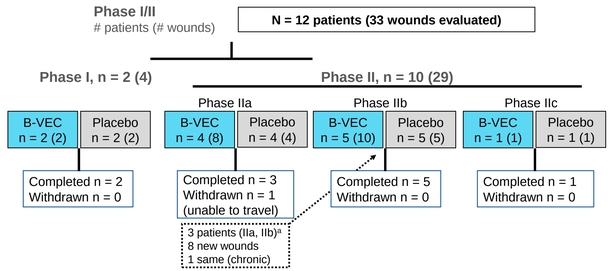
Introduction

- RDEB is a devastating skin disease caused by mutations in the *COL7A1* gene and characterized by widespread painful blistering, with no currently approved therapies
  - Previous RDEB corrective studies using *ex vivo*–based approaches are invasive[1-3], and direct in vivo gene transfer to skin has been viewed as an attractive alternative
- Beremagene geperpavec (B-VEC), is a modified, non-integrating HSV-1 vector containing two *COL7A1* genes, which has restored COL7 expression *in vitro* in RDEB keratinocytes and fibroblasts and has demonstrated molecular correction *in vivo* in COL7-deficient mice and primary human RDEB skin xenografts[4]
- The main objective of this study was to assess the safety of repeated topical B-VEC applications. This was measured by wound area reduction, time to and duration of wound closure, as well as molecular correction (restoration of COL7 expression including both NC1 and NC2 domains and anchoring fibril formation)

Methods

- A placebo-controlled, single-center, open-label, intra-patient trial assessed the safety and efficacy of B-VEC in patients ≥6 months of age with RDEB
- Nine patients with RDEB were enrolled in the trial, and three of the nine patients were re-enrolled from Phase IIa to IIb, for a total of 12 participants in the safety population (**Figure 1**)
- Target wounds of comparable size were treated with B-VEC or placebo
- Patients were evaluated periodically over 12 weeks in outpatient clinics, and off-treatment monitoring was continued for 12 additional weeks, with a long-term follow-up period of 5 years following the main study
- Safety assessments included adverse events and clinical laboratory values (biochemistry, hematology, urinalysis, anti-drug antibodies, viral shedding)
  - In Phase I, blood and urine samples were collected pre-dose and at all scheduled visits
  - To minimize patient discomfort, blood and urine evaluations were removed from Phase IIa but later reinstated in Phase IIb for additional safety data
  - In Phases IIA and IIB, treated sites were swabbed to monitor viral shedding

Figure 1. Patient Disposition (Safety Analysis)



[a]Patients were enrolled in Phase IIa as Patients 03, 05, and 06 and in Phase IIb as Patients 11, 08, and 07, respectively.

Results

Patient Demographics

- The safety data set included 7 adult and 5 pediatric patients of which 75% were male and 100% were White, with 25% being of Hispanic or Latino ethnicity
- 11 patients completed the trial, and 1 patient, 01-004, withdrew early due to travel inability
- Patient wounds were most commonly located on appendages
  - Surface area at baseline ranged from 0.89 cm^2 to 65 cm^2

Table 1. B-VEC Extent of Exposure

Patient	Age, y	Phase	B-VEC Dose (PFU/wound/ administration)	Number of B-VEC–treated Wounds	Study Days in Which Dosing Occurred
01	36	I	1e8	1	1, 3, 29, 31
02	28	I	1e8	1	1, 3, 15, 29, 31, 43
03	21	IIa	3e8	2	1, 2, 3, 4, 5, 16, 34
04	18	IIa	6e8	2	1, 2, 3, 4, 5
05	13	IIa	3e8	2	1, 2, 3, 4, 5, 36
06	14	IIa	3e8	2	1, 2, 3, 4, 5, 34, 41
07	15	IIb	2e8	2	1, 4, 6, 8, 11, 13, 15, 18, 29, 71, 98
08	14	IIb	2e8	2	1, 3, 5, 9, 12, 15, 17, 29, 64, 89
09	21	IIb	2e8	2	1, 2, 5, 8, 10, 12, 15, 33, 61, 92
10	33	IIb	2e8	2	1, 2, 5, 8, 10, 12, 15, 33, 64, 97
11	22	IIb	2e8	2	1, 2, 5, 8, 10, 12, 15, 33, 37, 38, 60, 92
12	10	IIc	8e8	1	Cycle 1: 1, 2, 5, 7, 8, 10, 11, 12, 14, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26 Cycle 2: 38, 39, 40, 41, 42, 43, 44, 46, 47, 48, 50, 51, 52, 53, 54, 55, 57, 58, 59, 60, 61

- B-VEC or placebo was administered topically to wounds in accordance with the study protocol; dosing of B-VEC is shown in **Table 1**

Table 2. Summary of Adverse Events for Topical B-VEC Application

Parameter	Events, n
Total number of adverse events (AEs)	21
Moderate AEs	1
Unrelated to treatment	1
Mild AEs	20
Unrelated to treatment	13
Unlikely related to treatment	1
Possibly related to treatment	4
Probably related to treatment	2

- No deaths or other serious AEs were reported, and all AEs resolved during the trial, with no events requiring dosing or frequency reduction (**Table 2**)
- Of the 129 topical B-VEC doses administered, 21 AEs were reported
  - Four possibly related mild AEs included fever, peculiar taste, rash, and itching
  - The 2 probably related mild AEs were application site discharge

Results (Cont'd)

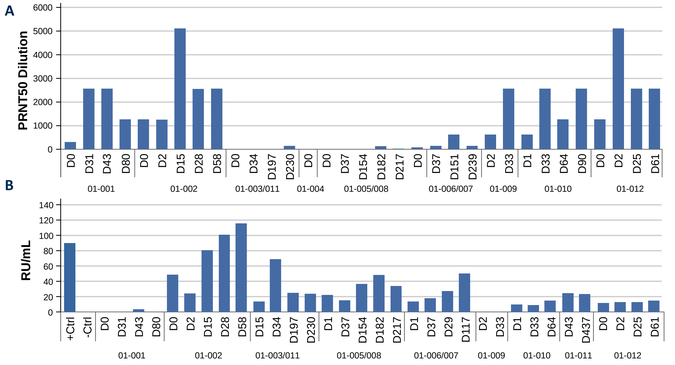
Table 3. Blood and Urine Samples Did Not Detect Vector Shedding in Phase I/IIb

Patient ID	Sample Type	Study Day	Assay Call[a]
01-001	Blood	0	< LOD
	Blood	2	< LOD
	Blood	28	Negative
	Blood	30	Negative
	Blood	42	< LOD
	Urine	0	< LOD
	Urine	2	Negative
	Urine	14	< LOD
01-002	Blood	0	< LOD
	Blood	2	< LOD
	Blood	14	< LOD
	Blood	28	Negative
	Urine	30	Negative
	Urine	0	Negative
	Urine	2	Negative
	Urine	14	Negative
	Urine	28	Negative
	Urine	30	< LOD
01-007	Blood	117	< LOD
01-008	Blood	60	Negative
01-009	Blood	30	Negative
01-010	Blood	30	< LOD
01-011	Blood	30	< LOD
01-007	Urine	117	< LOD
01-008	Urine	60	< LOD
01-010	Urine	30	< LOD
	Urine	60	< LOD
01-011	Urine	30	Negative
	Urine	60	< LOD

[a]<LOD = below level of detection.

- HSV-1 DNA was not detected in blood or urine samples evaluated during Phases I and IIb (**Table 3**)
- Additionally, low levels of viral copies were detected from skin swabs of application sites during dosing phases (Data not shown)
  - Minimal or no detectable copies were observed at Day 30 and Day 60 return visits

Figure 2. Quantification of HSV (A) and COL7 (B) Antibodies in Patient Sera



- HSV-1 antibodies were detected at variable levels before and after B-VEC administration but had no observable impact on treatment safety or efficacy (**Figure 2A**)
- Positive COL7 antibodies at baseline and a slight increase in post B-VEC treatment titers were observed in some patients (**Figure 2B**)
  - COL7 antibody levels had no observable impact on treatment safety or efficacy (Data not shown)

Conclusions

- **Repeated topical applications (129 total doses in 12 total participants across the phase I/II study) of B-VEC in patients with RDEB was well-tolerated**
- **There were no deaths or other serious AEs reported, and treatment-related AEs were mild**
- **Blood and urine samples collected for viral shedding analysis were negative**
- **HSV-1 antibodies were detected at variable levels before and after B-VEC administration but had no observable impact on treatment safety or efficacy**
- **Increased COL7 antibodies were only observed after dosing in 2 subjects, were variable in these subjects, and had no apparent impact on safety or efficacy**
- **A Phase III trial is ongoing to further evaluate the safety and efficacy of B-VEC vs placebo in patients with DEB**

References

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Disclosures

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