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ORIGINAL RESEARCH ARTICLE

Long-Term Safety and Tolerability of Beremagene Geperpavec-svdt (B-VEC) in an Open-Label Extension Study of Patients with Dystrophic Epidermolysis Bullosa

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Abstract

Background Patients with dystrophic epidermolysis bullosa have pathogenic variants in *COL7A1*, leading to skin fragility. Beremagene geperpavec-svdt (B-VEC) is a modified, herpes simplex virus type 1-based gene therapy vector that topically delivers *COL7A1* to dystrophic epidermolysis bullosa wounds. In a phase III study, B-VEC significantly improved wound healing at 3 and 6 months compared with placebo.

Objective We aimed to evaluate the safety and tolerability of B-VEC beyond 6 months in patients with dystrophic epidermolysis bullosa.

Methods An open-label extension study was conducted with 47 subjects (24 rollover from phase III; 23 treatment naïve) receiving B-VEC weekly to target wound areas for up to 112 weeks (median 81 weeks). Safety was assessed by adverse events. Treatment satisfaction and quality of life were assessed with patient-reported outcomes as exploratory measures of efficacy. Selected wounds from phase III rollover subjects were assessed for closure.

Results Thirty-five subjects (74.5%) reported one or more adverse events; most were mild or moderate in severity. Fourteen subjects experienced 17 serious adverse events and ten experienced 14 severe adverse events; none was considered treatment related. No adverse events led to treatment or study discontinuation. Patient-reported outcomes indicated high levels of treatment satisfaction, but were inconclusive with regard to quality of life. Among rollover subjects, wounds that received B-VEC during phase III maintained high closure rates during the open-label extension (range 61.1–89.5%, assessed baseline to month 12).

Limitations This was an open-label design, with a variable follow-up.

Conclusions Patients undergoing extended B-VEC treatment maintained high satisfaction and continued to respond to treatment with no new safety signals detected in the open-label extension study, supporting the continuous use of B-VEC.

Clinical Trial Registration NCT04917874 (date of trial registration: 8 June, 2021).

1 Introduction

Dystrophic epidermolysis bullosa (DEB) is a rare genetic disorder caused by pathogenic variants in the *COL7A1* gene encoding the basement membrane protein type VII collagen (COL7) [1]. COL7 proteins aggregate to form specialized basement membrane structures (anchoring fibrils), which augment tissue integrity in skin and stratified squamous mucosa [2]. The absence of functional COL7 in patients with DEB causes debilitating blisters, open wounds, and subsequent scarring of large areas [1, 3]. Dystrophic epidermolysis bullosa is inherited as autosomal recessive (RDEB) or autosomal dominant (DDEB), with RDEB presenting with more severe phenotypes [4]. The global prevalence of DEB is estimated between 3.5 and 20.4 cases per million [5–8].

Prior to 2023, only supportive care was available for DEB. This prompted the development of novel gene therapies to correct the genetic defect underlying DEB [9, 10]. The first corrective DEB treatment to receive US Food and Drug Administration approval is beremagene geperpavec-svdt (B-VEC; sold commercially as Vyjuvek®; Krystal Biotech, Inc., Pittsburgh, PA, USA), a topical gene therapy

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Key Points

The results of this open-label study build upon existing safety and tolerability data for beremagene geperpavec-svdt by demonstrating favorable outcomes beyond 6 months of treatment in children and adult patients with dystrophic epidermolysis bullosa.

Beremagene geperpavec-svdt was well tolerated, with no study or treatment discontinuations because of an adverse event; the majority of adverse events were mild or moderate in severity and were consistent with the type and frequency of adverse events observed in the phase III study.

Patient-reported outcome measures were indicative of treatment satisfaction, consistent with the durable closure of wounds or continued response to treatment in wounds that re-opened in rollover patients that were followed from the phase III study and reassessed.

that delivers *COL7A1* directly to DEB wounds. B-VEC is an engineered, non-replicating, herpes simplex virus type 1 vector encoding two copies of *COL7A1*. Preclinical studies with B-VEC supported initiation of a randomized, open-label, placebo-controlled, phase I/II trial (GEM-1; NCT03536143), demonstrating molecular correction and wound closure in B-VEC-treated skin [11].

The phase III, double-blind, intra-patient randomized, placebo-controlled trial (GEM-3; NCT04491604) included 31 patients aged 1–44 years who were treated weekly for 26 weeks with either B-VEC or placebo on matched wound pairs [12]. At 3 months, 71% of B-VEC-treated wounds showed complete wound healing compared with 20% of placebo-treated wounds; this was maintained at 6 months, with 67% complete wound healing for B-VEC-treated versus 22% of placebo-treated wounds. The only treatment-related adverse event (AE), erythema in one subject, was mild. B-VEC was well tolerated and no participants stopped treatment because of AEs [12]. At the time of approval, availability of long-term treatment data was limited. An open-label extension (OLE) study (NCT04917874) was conducted to provide extended access to phase III participants and collect additional health outcomes.

2 Methods

2.1 Patients

Forty-seven patients were enrolled into an OLE study of B-VEC, with 24 subjects receiving extended treatment following the phase III study (rollover) and 23 naïve subjects who were newly enrolled to receive treatment. All 47 subjects had a clinical diagnosis of DEB (45 RDEB, two DDEB).

2.2 Study Design

The OLE study was conducted at five centers across the USA in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Wounds were treated with B-VEC in designated target areas at a maximum weekly concentration of 10^9 plaque-forming units/mL for patients aged ≥ 3 years (2.0 mL); patients aged < 3 years received half the volume. This volume may have been utilized across several wounds of differing sizes during weekly application using a drop matrix technique to create an ~ 1 cm-by-1 cm grid. Target areas (of which there were 30) were standardized designated regions that encompassed the entire body, with a variable number of wounds within each area dependent on the subject's wound burden. Wounds within a selected target area were treated once weekly until wound closure before moving to a new target area. Treatment of target areas, as opposed to individual wounds that were far apart, was based on experience from the phase III study and the dynamic nature of DEB wounds. Study visits occurred weekly for up to 112 weeks, with a variable duration of treatment. Patients were not given placebo because of the efficacy of B-VEC observed in the phase III study.

2.3 Safety Assessments

Safety was evaluated by the frequency and severity of AEs. Only treatment-emergent AEs were collected. Treatment-emergent AEs were classified by severity (mild, moderate, severe, or life threatening) and relationship to treatment (not related, unlikely related, possibly related, or related) and were coded using the *Medical Dictionary for Regulatory Activities* version 25.0 system organ classes and preferred terms. Assessments were made by investigators based on their clinical experience in DEB patient care and the subject's medical history. Each treatment-emergent AE was counted once for each subject unless it resolved and recurred.

2.4 Patient-Reported Outcomes (PROs) and Wound Closure Assessments

Three patient-reported outcomes (PROs) were collected to assess treatment satisfaction and quality of life. The Treatment Satisfaction Questionnaire for Medication 9 (TSQM-9) measures patient satisfaction with treatment through nine items that encompass Effectiveness,

Convenience, and Global Satisfaction [13, 14]. Domain scores range from 0 to 100, with higher scores representing higher satisfaction in that domain. The TSQM-9 was completed by 22 rollover patients who were aged ≥ 18 years or their guardian at the first and last OLE study visits. Patients who were B-VEC naïve (17) completed the TSQM-9 only at the last study visit, as they had no prior B-VEC experience.

The second PRO tool, the Skindex-29, consists of 29 items addressing symptom, emotional, and functioning aspects of disease on quality of life [15, 16]. Patient responses are transformed to a linear scale of 100, with 0 indicating no effect and 100 indicating an effect experienced all the time. The scores are reported as three mean scale scores for the three domains. It was completed by 28 subjects who were aged ≥ 12 years at the week 1, 26, 39, 52, 78, and 104 visits. Not all participants completed all visits because of variability in the follow-up time associated with early termination of the study when B-VEC received Food and Drug Administration approval.

The third PRO tool, the EuroQol 5-Dimension (EQ-5D), is a short descriptive system questionnaire (EQ-5D-5L) and a visual analog scale (EQ VAS) that assesses five areas (Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression) as a measure of general health status. It was completed by 28 subjects who were aged ≥ 12 years at the week 1, 26, 39, 52, 78, and 104 visits. Because of termination of the study following B-VEC marketing approval, not all final assessments were completed at the scheduled timepoint; these assessments were reassigned to the nearest timepoint for analysis.

Rollover subjects had assessments made for the B-VEC-treated wound from the primary efficacy wound pair in the phase III study to assess continued durability. This single wound area was assessed to be open or closed, defined as complete closure of the exact wound area selected at baseline of the phase III study, specified as skin re-epithelialization without drainage. Investigators completed their assessments comparing the image of the baseline wound from the phase III study to the images collected at the 3-, 6-, 9-, and 12-month visits of the OLE study. Participants who missed multiple treatment visits were excluded from this assessment.

2.5 Statistical Analysis

No formal hypothesis testing was pre-specified for the OLE study; only descriptive analyses were planned. Stratified analyses were performed for rollover and naïve subjects.

3 Results

3.1 Patients

Demographic and baseline characteristics for the 47 subjects are summarized in Table 1. Most subjects (87.2%) either completed the OLE study or discontinued and transitioned to the commercial product when B-VEC received Food and Drug Administration approval (Table S1 and Fig. S1 of the Electronic Supplementary Material [ESM]). Five subjects withdrew from the study; three for reasons related to difficulty traveling to the study site, one for challenges with increased dressing changes outside of the home setting, and one to focus on clinical management of recurrent squamous cell carcinoma, which was unrelated to B-VEC. The age of subjects ranged from 6 months to 46 years (median 16.7 years). Twenty-six subjects (55.3%) were aged 18 years or younger; two naïve subjects were below 1 year of age. Two subjects had DDEB (one naïve, one rollover). The majority of subjects were White (68.1%), but two naïve subjects were Black. The median duration of study treatment in the OLE was 565 days (> 1.5 years), with the longest duration of treatment equaling 794 days (~ 2.2 years). Over half of all participants had over 1 year of exposure (61.7%). The duration of exposure was longer for rollover subjects than for naïve subjects, consistent with their earlier enrollment and further progression into the study prior to termination (Table 1).

3.2 Safety

Among all subjects, 74.5% reported at least one AE, the majority of which were mild or moderate in severity (Table 2). Two treatment-emergent AEs, mild bleeding at the wound surface, were reported in the same subject and were possibly related to treatment; both instances resolved within the same day they began. Fourteen subjects (nine rollover, five naïve) reported 17 serious AEs and ten subjects (eight rollover, two naïve) reported 14 severe AEs; all were assessed as unrelated to treatment. Details can be found in the ESM (Table S2 of the ESM). There were no deaths and no AEs that led to discontinuation of the study or treatment. The most common AEs (reported in ≥ 10% of subjects) were coronavirus disease 2019 (31.9%), cough (19.1%), pyrexia (14.9%), skin infection (12.8%), and vomiting (10.6%) [Table 2]. None of these commonly observed AEs was considered related to treatment. These types of AEs resembled those reported during the phase III study [12] and were consistent with common symptoms of DEB [17].

Table 1 Subject demographic characteristics and duration of beremagene geperpavec-svdt exposure

	Rollover subjects ($N = 24$)	Naïve subjects ($N = 23$)	All subjects ($N = 47$)
Age (years, at the OLE week 1 visit)			
Mean (SD)	16.7 (10.1)	16.3 (11.5)	16.5 (10.7)
Median (Min, Max)	16.5 (2.0, 35.0)	16.7 (0.5, 45.9)	16.7 (0.5, 45.9)
Sex, *n* (%)			
Male	18 (75.0)	12 (52.2)	30 (63.8)
Female	6 (25.0)	11 (47.8)	17 (36.2)
Age by category (%)			
≤ 6 months	0	1 (4.3)	1 (2.1)
> 6 months and ≤ 3 years	1 (4.2)	3 (13.0)	4 (8.5)
> 3 and ≤ 6 years	3 (12.5)	1 (4.3)	4 (8.5)
> 6 and ≤ 12 years	5 (20.8)	4 (17.4)	9 (19.1)
> 12 and ≤ 18 years	4 (16.7)	4 (17.4)	8 (17.0)
> 18 years	11 (45.8)	10 (43.5)	21 (44.7)
Race, *n* (%)			
White	17 (70.8)	15 (65.2)	32 (68.1)
Black	0	2 (8.7)	2 (4.3)
Asian	2 (8.3)	2 (8.7)	4 (8.5)
American Indian or Alaska Native	5 (20.8)	3 (13.0)	8 (17.0)
Unknown	0	1 (4.3)	1 (2.1)
Ethnicity, *n* (%)			
Hispanic or Latino	13 (54.2)	8 (34.8)	21 (44.7)
Not Hispanic or Latino	11 (45.8)	15 (65.2)	26 (55.3)
Overall exposure duration (days)			
Mean (SD)	602.1 (229.7)	342.7 (197.1)	475.1 (249.3)
Median (Min, Max)	642.0 (1, 794)	344.0 (21, 664)	565.0 (1, 794)
Total number of doses received			
Mean (SD)	62.1 (32.3)	34.5 (20.1)	48.6 (30.2)
Median (Min, Max)	72.5 (1, 107)	36.0 (3, 73)	48.0 (1, 107)

Exposure duration: from the first dose date to the last dose date

Max maximum, *Min* minimum, *OLE* open-label extension, *SD* standard deviation

3.3 PROs and Wound Closure

Patient-reported outcome measures were used to assess treatment satisfaction (TSQM-9) and quality of life (Skindex-29 and EQ-5D). The mean TSQM-9 scores at the first and last visit of the OLE study for rollover subjects are presented graphically in Fig. 1a. For the three domains, the mean scores were generally high (> 65) post-phase III (OLE week 1 visit) and remained high at the last study visit (68.3, standard deviation [SD] ± 20.56 for Effectiveness, 76.3 ± 19.23 for Convenience, and 75.9 ± 18.78 for Global Satisfaction). The mean change from week 1 to the last study visit was minimal (2.5 for Effectiveness, 1.5 for Convenience, and −3.4 for Global Satisfaction), indicating that participants maintained high satisfaction with B-VEC from the end of the phase III study throughout the OLE. Individual scores for rollover patients from post-phase III to the last study visit are also presented (Fig. 1c–e). Naïve participants showed similar mean scores at their last study visit (70.9 ± 19.89 for Effectiveness, 68.3 ± 19.42 for Convenience, and 80.7 ± 15.31 for Global Satisfaction), suggesting similar levels of treatment satisfaction between the naïve and rollover groups (Fig. 1b).

For participants aged 12 years or older, the Skindex-29 was completed at baseline (week 1 OLE visit) and at the indicated weeks. Because of early study termination, less than half of participants aged ≥ 12 years completed the assessment beyond week 52. The mean score over time for the different domains is shown in Fig. 2a. For the Skindex-29, a lower score is indicative of less impairment, meaning a decrease from baseline represents an improvement. While not statistically significant, scores trended downward from baseline to week 104 (54.7 ± 28.4 for Emotions, 50.3 ± 26.3 for Functioning, 61.9 ± 21.4 for Symptoms, 54.8 ± 25.2 Total), which may suggest an improvement in skin-specific quality of life for the study participants. The mean

Table 2 Summary of adverse events over the treatment period

	Rollover subjects ($N = 24$)		Naïve subjects ($N = 23$)		All subjects ($N = 47$)	
	n (%)	Events	*n* (%)	Events	*n* (%)	Events
Subjects with at least 1, *n* (%)						
TEAE	17 (70.8)	102	18 (78.3)	72	35 (74.5)	174
Drug-related TEAE	0	0	1 (4.3)	2	1 (2.1)	2
Severe TEAE	8 (33.3)	12	2 (8.7)	2	10 (21.3)	14
Serious TEAE	9 (37.5)	11	5 (21.7)	6	14 (29.8)	17
Drug-related serious or severe TEAE	0	0	0	0	0	0
AE leading to premature discontinuation of treatment or study	0	0	0	0	0	0
Deaths, *n* (%)	0	0	0	0	0	0
TEAEs reported for at least 5% of subjects by system organ class						
Infections and infestations						
Coronavirus disease 2019	9 (37.5)	9	6 (26.1)	8	15 (31.9)	17
Skin infection	4 (16.7)	4	2 (8.7)	4	6 (12.8)	8
Cellulitis	3 (12.5)	4	1 (4.3)	1	4 (8.5)	5
Rhinitis	3 (12.5)	3	1 (4.3)	1	4 (8.5)	4
Wound infection	2 (8.3)	2	1 (4.3)	2	3 (6.4)	4
Respiratory, thoracic, and mediastinal disorders						
Cough	6 (25.0)	8	3 (13.0)	3	9 (19.1)	11
Rhinorrhea	2 (8.3)	2	2 (8.7)	2	4 (8.5)	4
General disorders and administration site conditions						
Pyrexia	5 (20.8)	7	2 (8.7)	2	7 (14.9)	9
Gastrointestinal disorders						
Vomiting	2 (8.3)	2	3 (13.0)	3	5 (10.6)	5
Diarrhea	2 (8.3)	2	1 (4.3)	1	3 (6.4)	3
Metabolism and nutrition disorders						
Dehydration	2 (8.3)	2	1 (4.3)	1	3 (6.4)	3

AE adverse event, *TEAE* treatment-emergent adverse event

change from baseline to week 104 was 0.6 for Emotions, −5.6 for Functioning, −6.9 for Symptoms, and −4.0 Total (a negative change is indicative of improvement). However, these scores remain severe [18] and are limited by the number of participants in the later timepoints. Additionally, mean scores were higher than baseline at the week 78 visit, and overall, the large SD values make interpretation difficult. Individual Skindex-29 scores over time, presented as heat maps (Fig. 2b–i), are similarly difficult to interpret for both rollover (Fig. 2b–e) and naïve (Fig. 2f–i) subjects. Mean Skindex-29 scores analyzed separately by rollover and naïve subjects can be found in the ESM (Fig. S2 of the ESM).

The EQ-5D was completed by participants aged ≥ 12 years at baseline (OLE week 1) and at the indicated weeks. The EQ VAS component is a continuous measure that ranges from 0 to 100, with higher scores representing better health status. A study of European patients with DEB reported an average EQ VAS score of 61.9 [19]. Mean scores demonstrated a numerical trend toward improvement from baseline (64.7 ± 18.8) to week 104 (76.7 ± 15.4), with a mean change from baseline to week 104 of 12.0 (Fig. 3a). EQ VAS scores analyzed separately for rollover and naïve subjects show similar trends, with mean scores higher than baseline at every visit assessed (Fig. S2 of the ESM); scores by individual subject over time are presented in Fig. 3b–c. The EQ-5D-5L (categorical) component of the PRO reflected high levels of impairment across multiple dimensions, with no consistent pattern of change (data not shown). Interpretation of the EQ-5D is limited by the number of participants at later timepoints.

Wound closure status was collected for rollover subjects for primary wounds previously treated with B-VEC during the phase III study. Selected wounds in target areas were assessed at the start of phase III, at the end of phase III, and throughout the OLE. Out of 24 rollover subjects, 19 were evaluated; data were not available for five subjects without consistent follow-up visits. Complete wound closure, reported at each visit for 16–19 subjects, ranged from 61.1 to 89.5% in the OLE study (Fig. 4). The proportion of subjects with complete wound closure during the OLE study was

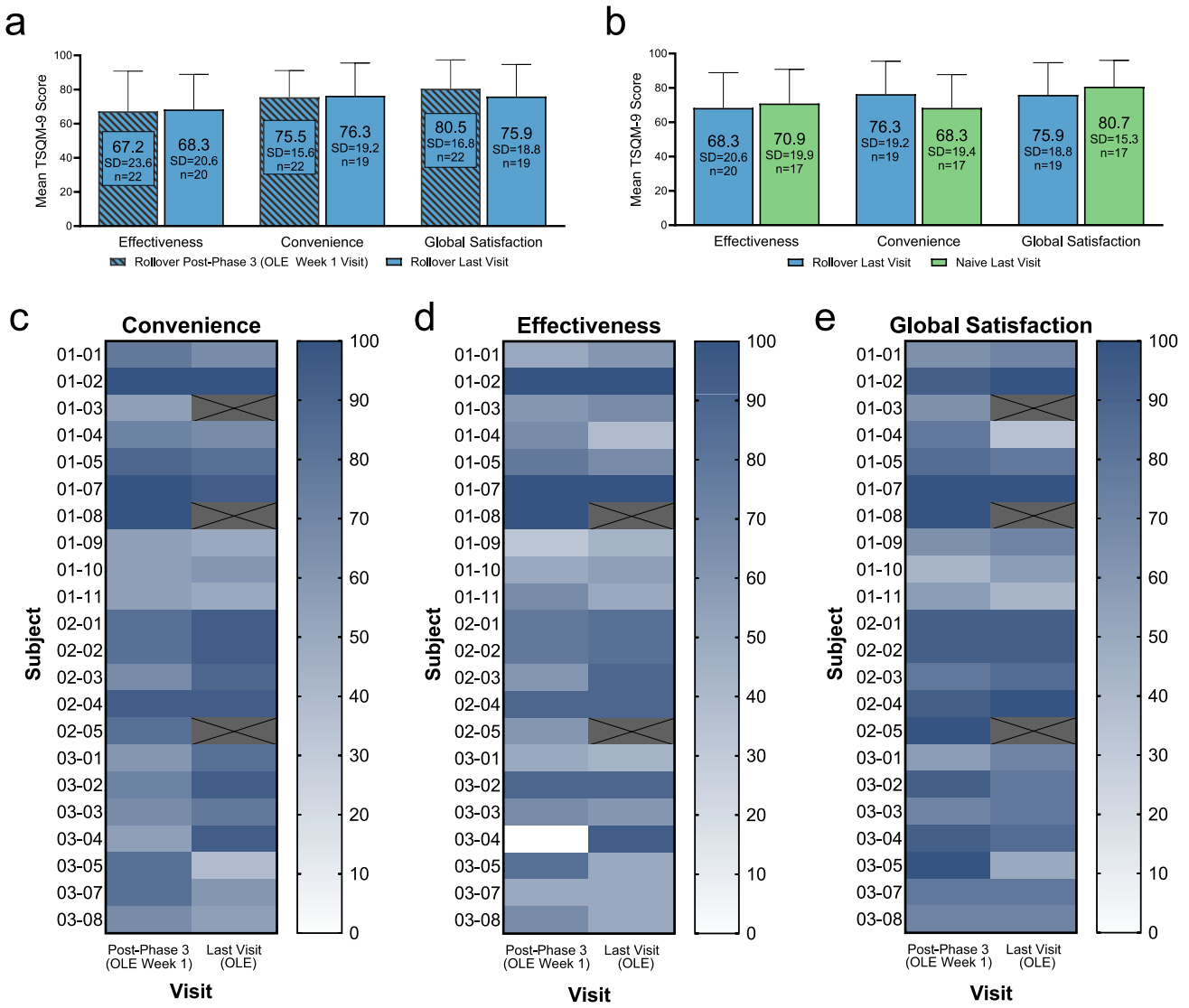

Fig. 1 Mean and individual Treatment Satisfaction Questionnaire for Medication 9 (TSQM-9) scores over time. (**a**) Mean TSQM-9 scores over time for rollover subjects at the OLE study first (post-phase III; *blue with dashed lines*) and last (*blue*) visit and (**b**) mean TSQM-9 scores at the last study visit for rollover (*blue*) and naïve (*green*) subjects. A higher mean score correlates with higher treatment satisfaction in each domain. The standard deviation (SD) and number of subjects (*n*) is indicated. (**c–e**) Individual TSQM-9 scores for rollover subjects post-phase III (OLE week 1) and at the last OLE visit for the (**c**) Convenience, (**d**) Effectiveness, and (**e**) Global Satisfaction domains. A *gray crossed-out box* indicates that a score was not reported at that timepoint. *n* number of subjects, *OLE* open-label extension, *SD* standard deviation

consistent with months 3 (68.4%) and 6 (73.7%) in the phase III study.

In addition, despite not reaching 100% closure, many wounds (designated as primary or secondary in the phase III study) demonstrated significant long-term improvement. Figure 5 provides examples of wounds in selected rollover subjects with RDEB at the beginning of phase III, the end of phase III, and the end of the OLE study. Figure 6 provides an example of wound healing in a naïve subject with RDEB after 1 year in the OLE study. Wound healing in a naïve patient with DDEB can be found in the ESM (Fig. S3 of the ESM). These images illustrate the continued improvement in wound closure with extended B-VEC treatment during the OLE.

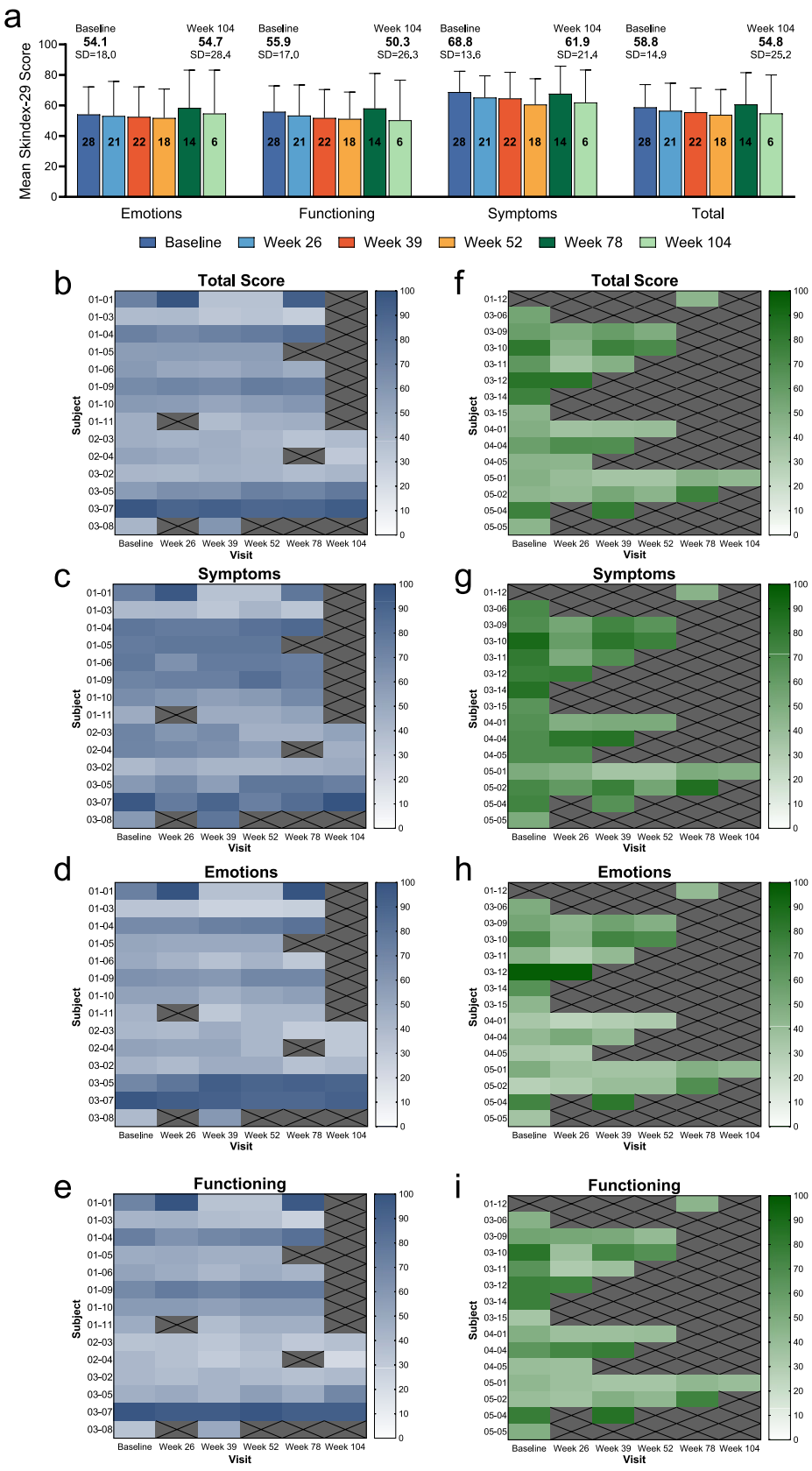

Fig. 2 Mean and individual Skindex-29 scores over time. (**a**) Mean Skindex-29 score (skin-specific quality of life) is indicated at the first open-label extension visit (baseline) and the indicated weeks for the three domains and total mean score for all assessed subjects (naïve and rollover). A lower score indicates less impairment, thus a decrease from baseline (open-label extension week 1) represents improvement. The mean score and standard deviation (SD) are reported for baseline and week 104; the number of subjects is indicated within each bar. (**b–i**) Individual Skindex-29 scores over time for (**b–e**) rollover (*blue*) and (**f–i**) naïve (*green*) subjects. Heat maps display individual scores at the indicated timepoints for (**b, f**) Total, (**c, g**) Symptoms, (**d, h**) Emotions, and (**e, i**) Functioning domains of Skindex-29 score. A *gray crossed-out box* indicates a score was not reported at that timepoint

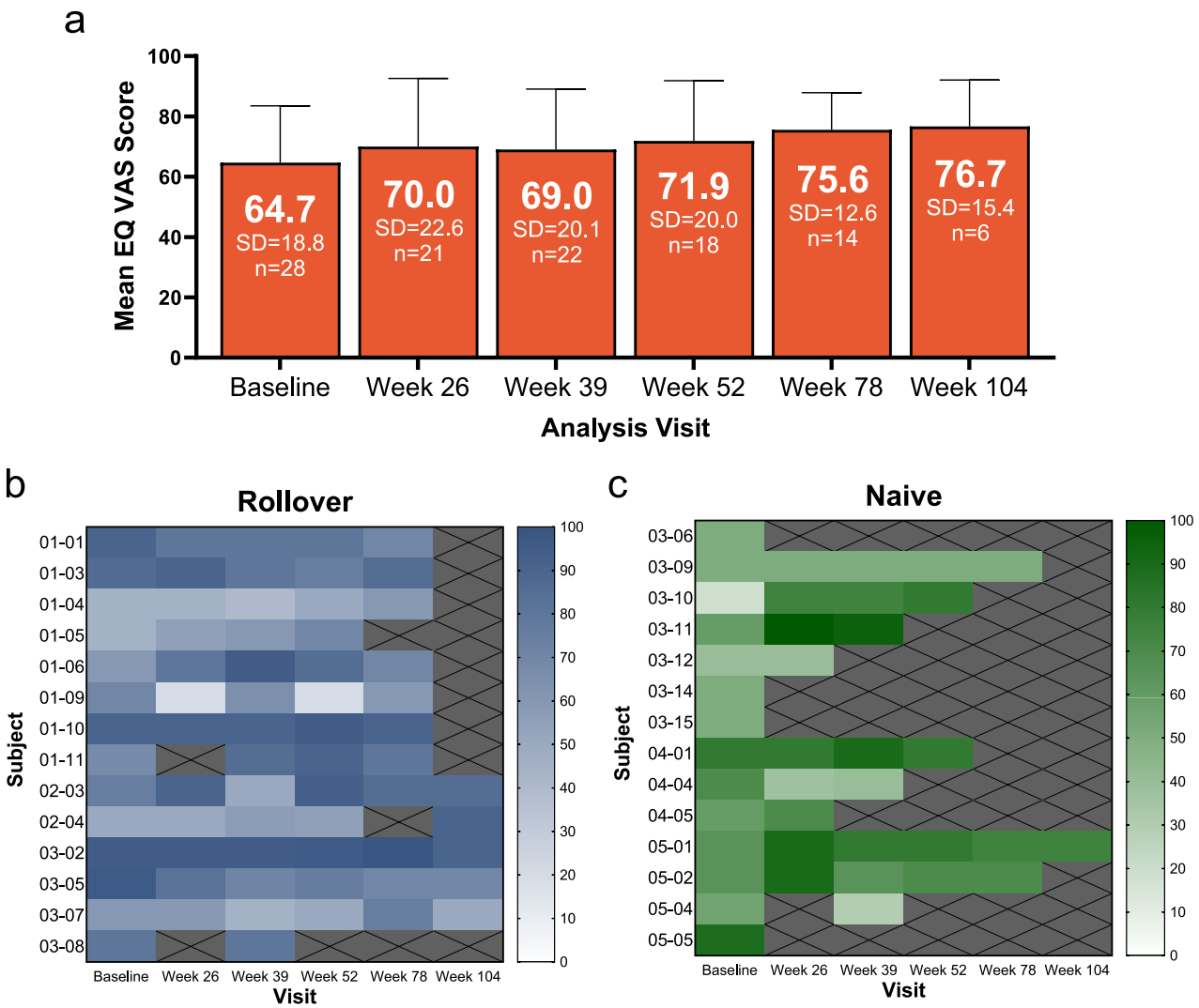

Fig. 3 Mean and individual EuroQol visual analog scale (EQ VAS) scores over time. (**a**) Mean scores for pooled rollover and naïve subjects. EQ VAS general health status is indicated at baseline (open-label extension week 1) and the indicated timepoints. A higher score correlates with better reported health status. The standard deviation (SD) and number of subjects (*n*) are indicated. (**b, c**) Individual EQ VAS scores over time for (b) rollover (*blue*) and (c) naïve (*green*) subjects. A *gray crossed-out box* indicates a score was not reported at that timepoint

4 Discussion

The OLE study provides valuable B-VEC safety and tolerability data beyond the initial 6 months of exposure in the pivotal phase III study. Exposure in the OLE was substantially longer than in the phase III study, extending the duration of treatment beyond 2 years in seven subjects, without any new safety concerns. Among rollover subjects, the reassessment of wounds treated in phase III was consistent with continued efficacy and durable wound closure. A portion of wounds that demonstrated initial closure at month 3 or 6 of the OLE study (7/19 assessed wounds; 36.8%) remained closed throughout the entire OLE study, demonstrating durable closure. However, other wounds demonstrated the durable efficacy of B-VEC by their continued response to treatment upon re-opening. Because DEB wounds are dynamic and can re-open in the case of minor friction, the ability of wounds to demonstrate closure again is highly relevant when considering the use of B-VEC long term. The OLE also expanded upon the demographic population treated in phase III by enrolling new patients.

In general, the type and frequency of AEs observed in the OLE study were consistent with those previously observed. Similar to phase III, the majority of AEs reported were mild or moderate in severity. Coronavirus disease 2019 was the most frequent infection, which was expected given that the study occurred during the pandemic. Importantly, no serious AEs or severe AEs were

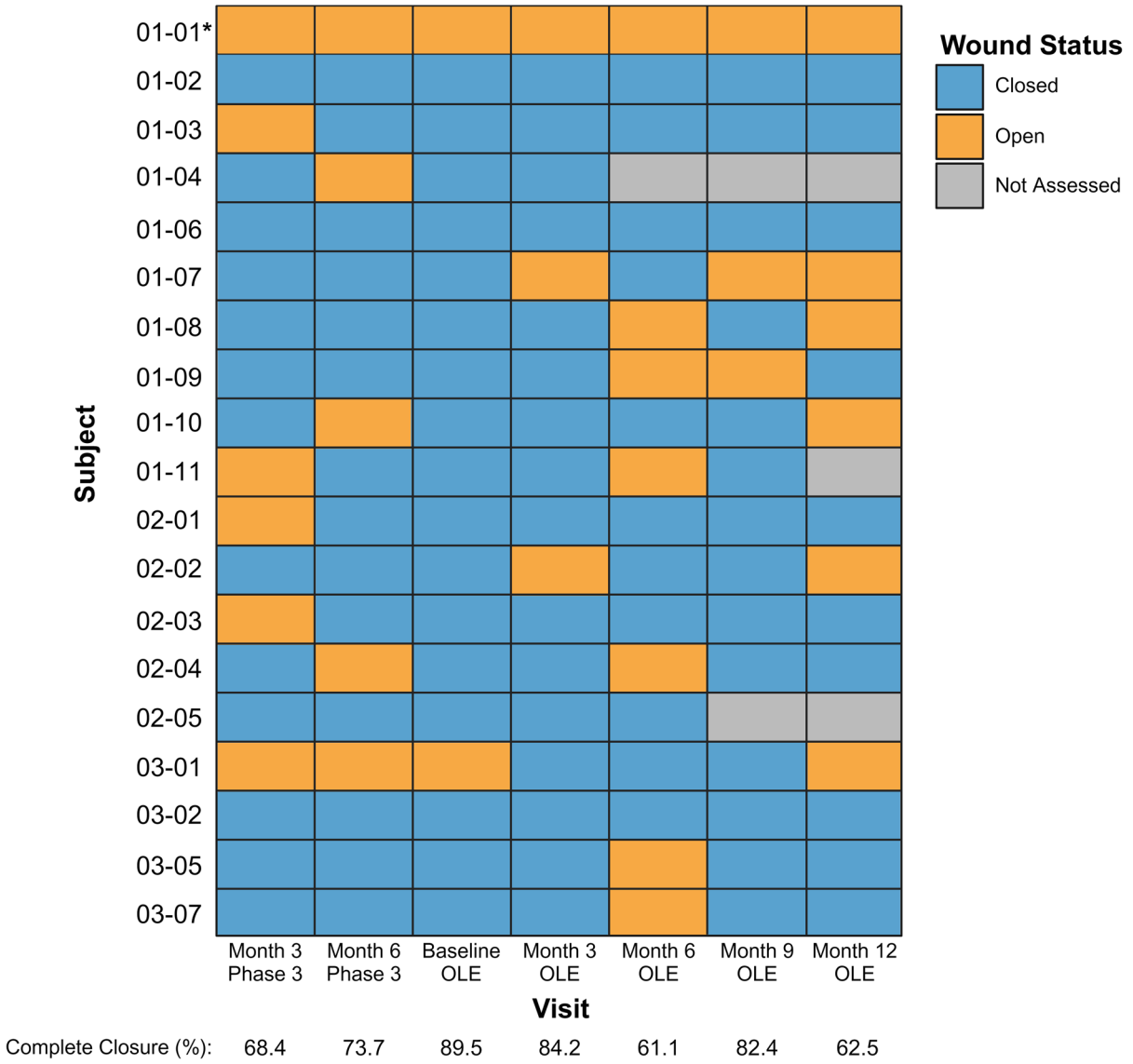

Fig. 4 Closure of beremagene geperpavec-svdt-treated primary wounds from the phase III study in rollover subjects. The beremagene geperpavec-svdt-treated wound from the primary efficacy wound pair (phase III study) was assessed at specified timepoints for wound healing (100% complete closure). The percentage of subjects with complete closure at each timepoint is indicated at the bottom. *While this subject did not achieve 100% wound closure at any of the assessed timepoints, this large wound (encompassing much of the subject's leg) demonstrated considerable re-epithelialization throughout the study. *OLE* open-label extension

considered related to B-VEC, and there were no deaths or AEs that led to discontinuation of treatment. Because of the longer follow-up time, the number of subjects reporting any AEs was slightly higher in the OLE study; however, these AEs were expected given the nature of DEB [17, 20] and similar to those reported in the phase III study [12]. Moreover, between rollover and treatment-naïve subjects, there were no notable safety differences.

Prospective studies of PRO measures in DEB are lacking. In the OLE study, we performed longitudinal assessments of treatment satisfaction, skin-specific quality-of-life, and general health status. TSQM-9 treatment satisfaction was high among subjects that rolled over from the phase III study and remained high during the course of the OLE study; it was also high among treatment-naïve subjects at their last visit. However, the positive results with respect to wound healing did not translate into significantly increased quality of life as assessed through the Skindex-29 and EQ-5D. It is possible that because the entire body surface is not undergoing weekly treatment, there was only a small impact

Fig. 5 Wound healing in selected rollover patients with recessive dystrophic epidermolysis bullosa. Images taken at the initiation of phase III (phase III baseline), the end of phase III (6 months), and the end of the open-label extension study for different target wound areas on the (**a**) lower back, (**b**) back, (**c**) upper back, (**d**) knee, and (**e**) thigh of five different patients with recessive dystrophic epidermolysis bullosa who received regular treatment with beremagene geperpavec-svdt

on Skindex-29 and EQ-5D; some subjects may have initially had fewer wounds that closed completely, while others may have had a larger initial wound burden and thus still had open wounds at the end of the study. Additionally, wound healing can be accompanied by pain and itch [21, 22]; thus, even if wounds are healing properly, this may affect reporting of skin quality and general health. Patients will continue to experience the extracutaneous manifestations and comorbidities of DEB, which may also be influencing the overall minimal change in scores. Additional outcomes, such as measures of pruritus and stratification by initial wound burden, may be helpful in future research to provide clarity to the scores reported here.

When interpreting the data in the study, limitations in the observational open-label study design need to be considered. Unlike phase III, there were no control wounds in the OLE study. As the OLE study was terminated early because of the commercial availability of the product, subjects had variable follow-up times. Consequently, only limited data were available for assessments beyond 12 months (i.e., weeks 78 and 104), limiting conclusions from later timepoints.

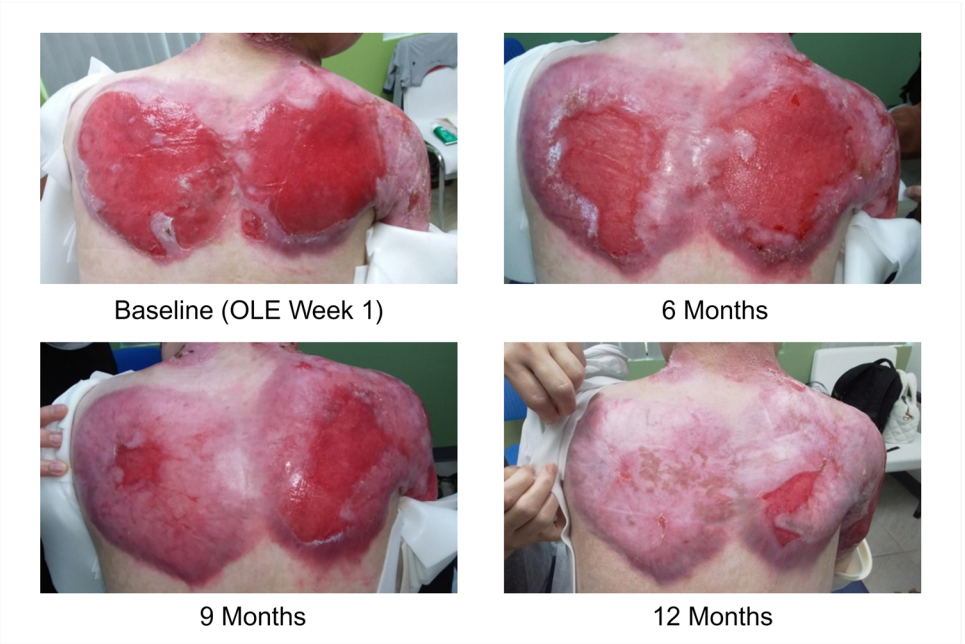

Fig. 6 Wound healing in a selected naïve patient with recessive dystrophic epidermolysis bullosa. Images taken at the initiation of the open-label extension study (baseline) and after 6, 9, and 12 months of beremagene geperpavec-svdt treatment on a large upper back wound

5 Conclusions

Collectively, the clinical response to B-VEC demonstrated in the OLE was consistent with the phase III trial [12]. The results of the OLE study provide long-term data in a broader population and do not present any new safety signals for the use of B-VEC. The continued safety and improvement in wound closure, including extended closure or the capacity for re-closure, upon long-term B-VEC administration highlight its unique properties compared to other therapies, for which severe immune reaction potentials often limit therapeutic attempts to single applications [23]. Overall, the benefit-risk profile of B-VEC supports the continued long-term treatment of children and adults with DEB.

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Declarations

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Conflicts of Interest M. Peter Marinkovich has undertaken paid consultancy for Amryt Pharmaceuticals DAC and is an investigator for Abeona, Castle Creek Biosciences, and Krystal Biotech, through funding administered by Stanford University Office of Sponsored Research. Amy S. Paller has been an investigator for AbbVie, Arcutis, Dermavant, Eli Lilly, Incyte, Janssen, Krystal Biotech, and UCB; a consultant for BioCryst, Boehringer-Ingelheim, Bristol Myers Squibb, Dermavant, Johnson & Johnson, Krystal Biotech, LEO Pharma, Mitsubishi Tanabe Pharma, Novartis, Primus Pharmaceuticals, Procter and Gamble, Regeneron, Sanofi/Genzyme, TWI Biotechnology, and UCB; and is on the data safety monitoring board for AbbVie, Abeona, Catawba, and Galderma. Amy S. Paller is an Editorial Board member of the *American Journal of Clinical Dermatology*; she was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Shireen V. Guide has been an investigator for Arcutis, Boehringer-Ingelheim, Castle Biosciences, Dermavant, Incyte, Jeune, Krystal Biotech, Novartis, Pfizer, and Sanofi, and a consultant and speaker for Krystal Biotech. Mercedes E. Gonzalez has been an investigator for AbbVie, Arcutis, Amgen, Anterogen, Dermavant, Eli Lilly, Incyte, Krystal Biotech, Neilsen Biosciences, Novartis, Regeneron, and Sanofi; a consultant with honorarium for Abeona, Apogee, Arcutis, Alphyn, Dermavant, Eli Lilly, Incyte, Krystal Biotech, and Verrica Pharmaceuticals, and on the speaker's bureau for Verrica Pharmaceuticals, Regeneron, Sanofi, Genzyme, Eli Lilly, Abbvie, Pfizer, and Krystal Biotech. Anne W. Lucky has been an investigator for Krystal Biotech and Phoenicis. Işın Sinem Bağcı has been an investigator for Castle Creek Biosciences and Krystal Biotech. Brittani Agostini, Kolleen Fitzgerald, Meghan M. Conner, and Suma M. Krishnan are employees and shareholders of Krystal Biotech. Shijie Chen and Hubert Chen were employees and shareholders of Krystal Biotech at the time of the analysis.

Ethics Approval This study was performed in accordance with the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines, and other applicable laws and regulations. Approval was obtained from the Stanford University Administrative Panel on Human Subjects in Medical Research (Site 1), Advarra (Sites 2 and 3), the Cincinnati Children's Institutional Review Board (Site

4), and the Ann & Robert H. Lurie Children's Hospital of Chicago Institutional Review Board (Site 5).

Consent to Participate All participants gave written informed consent/assent to participate in the research. At least one parent or guardian for each adolescent patient provided written informed consent.

Consent for Publication Patients signed an informed consent regarding publishing their data and photographs.

Availability of Data and Material All requests for data will be reviewed by the clinical sites and the study sponsor, Krystal Biotech, to verify whether the request is subject to any intellectual property or confidentiality obligations. Requests for access to the patient-level data from this study can be submitted via e-mail to medinfo@krystalbio.com with detailed proposals for approval. A signed data access agreement with the sponsor is required before accessing shared data.

Code Availability Not applicable.

Authors' Contributions All authors meet the International Committee of Medical Journal Editors criteria for authorship of this article. Study conception and design: SMK and HC; acquisition, analysis, and interpretation of data: MPM, ASP, SVG, MEG, AWL, and ISB; analysis of data: SC; supervision: SMK and BA; technical support: KF; formal analysis and writing (original draft preparation): MMC. All authors contributed to the critical revision of the manuscript for important intellectual content and approved the final version.

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