Prademagene zamikeracel for recessive dystrophic epidermolysis bullosa wounds (VIITAL): a two-centre, randomised, open-label, intrapatient-controlled phase 3 trial

Jean Y Tang, M Peter Marinkovich, Karen Wiss, Daniel McCarthy, Amanda Truesdale, Albert S Chiou, Edward Eid, Joyce K McIntyre, Irene Bailey, Louise K Furukawa, Emily S Gorell, Nicki Harris, Rohit K Khosla, H Peter Lorenz, Ying Lu, Jaron Nazaroff, I Dmitriy Grachev, Amanda J Moore

Summary

Background Recessive dystrophic epidermolysis bullosa (RDEB) is a rare genetic skin disease caused by mutations in the *COL7A1* gene encoding type VII collagen. Individuals with RDEB have fragile skin and most develop large, chronic wounds. The aim of the VIITAL study was to evaluate the efficacy and safety of a one-time surgical application of prademagene zamikeracel in wound healing.

Methods This randomised, open-label, intrapatient-controlled, phase 3 trial was conducted at two institutions in the USA. Eligible patients were aged 6 years or older, had a confirmed clinical and genetic diagnosis of RDEB, at least two chronic wounds (>20 cm²), had no evidence of an immune response to type VII collagen, and expressed the amino-terminal NC1 fragment of type VII collagen. Large, chronic wounds on the participants were matched in pairs by size, chronicity, and anatomical region and computer randomised (1:1) to treatment (prademagene zamikeracel) or control (standard of care). There was no masking. Prademagene zamikeracel is an autologous *COL7A1* gene-modified cellular sheet that is sutured onto to a large, chronic RDEB wound. A maximum of six wounds could be treated with prademagene zamikeracel per patient. The coprimary endpoints were the proportion of wounds with at least 50% healing and pain reduction from baseline at week 24 in the intention-to-treat population of all patients and their randomised wounds. The safety analysis population included all patients and evaluated wounds, randomised and non-randomised. This completed trial was registered with ClinicalTrials.gov (NCT04227106).

Findings Between Jan 1, 2020, and March 31, 2022, 15 patients were screened and 11 were enrolled (43 randomised wound pairs). Four (36%) of 11 participants were male and seven (64%) of 11 participants were female, with a median age of 21 years (IQR 17–30). 86 wounds were matched and randomised: 43 (50%) to prademagene zamikeracel and 43 (50%) to control. At week 24, 35 (81%) of 43 treated wounds were at least 50% healed from baseline for prademagene zamikeracel compared with seven (16%) of 43 control wounds (mean difference 67% [95% CI 50 to 89]; p<0·0001). The mean change from baseline to week 24 in wound pain was –3·07 with prademagene zamikeracel and –0·90 in controls (mean pairwise difference –2·23 [–3·45 to –0·66]; p=0·0002). No serious treatment-related adverse events were observed.

Interpretation Prademagene zamikeracel improved wound healing and pain versus control and was well tolerated, supporting its potential to reduce wound burden in patients with large, chronic RDEB wounds.

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Stanford University School of Medicine, Stanford, CA, USA (Prof J Y Tang MD, M P Marinkovich MD, A S Chiou MD, E Eid MD, I Bailey AIMBS, L K Furukawa MD, N Harris BA, Prof R K Khosla MD, Prof H Peter Lorenz MD, Prof Y Lu PhD, J Nazaroff MD); **VA Palo Alto Health Care System, Palo Alto, CA, USA** (M P Marinkovich); **University of Massachusetts Chan Medical School, Worcester, MA, USA** (Prof K Wiss MD, J K McIntyre MD); **Abeona Therapeutics, Cleveland, OH, USA** (D McCarthy BS, A Truesdale MA, I D Grachev MD, A J Moore MSHS); **Department of Dermatology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA** (E S Gorell DO)

Correspondence to: Prof Jean Y Tang, Stanford University School of Medicine, Stanford, CA 94063, USA **tangy@stanford.edu**

Introduction

Recessive dystrophic epidermolysis bullosa (RDEB) is a rare genetic skin disease characterised by painful blistering, wounds, and scarring that occur after minor skin trauma.[1–3] RDEB is caused by mutations in *COL7A1*, the gene encoding type VII collagen.[1,2] Without functional type VII collagen protein, slight pressure or trauma can shear the epidermis from the dermis.[1,4] Chronic wounds predispose patients with RDEB to infection, sepsis, anaemia, and cutaneous squamous cell carcinomas, which are aggressive and often lethal.[1,3,5,6]

RDEB treatment had been limited to supportive care, including extensive wound dressing changes, management of pain and itch, and treatment of frequent infections.[2,7] Bone marrow transplantation,[8] gentamicin,[9,10] and stem cells[11,12] have been evaluated in small trials with limited response. In the past 3 years, topical beremagene geperpavec (Vyjuvek) and birch bark triterpenes (Filsuvez) were approved by the US Food and Drug Administration (FDA) and the European Medicines Agency for the treatment of dystrophic epidermolysis bullosa wounds.[13,14] However, the wounds treated by these two drugs were mostly small (less than 20 cm²) and both treatments required repeated application. There are no approved treatments that have shown both sustained wound healing and pain reduction for large, chronic RDEB wounds.[13,14]

Research in context

Evidence before this study

Recessive dystrophic epidermolysis bullosa (RDEB) is a rare, genetic skin and multiorgan disease due to *COL7A1* mutations characterised by mucocutaneous blistering and scarring leading to a profound increase in morbidity and mortality. Up until 2023, standard of care treatment for skin blisters and wounds primarily involved supportive care such as daily bandaging and other palliative measures. Large, chronic wounds cause the most pain and itch and are the most clinically relevant symptom in patients with RDEB. In 2023, two novel topical therapies were approved by the US Food and Drug Administration for the treatment of RDEB wounds: a weekly gene therapy gel delivering corrected *COL7A1* (beremagene geperpavec, Vyjuvek) and a botanical extract derived from birch bark (birch bark triterpenes, Filsuvez). However, effectiveness and durability of these therapies on both wound healing and pain reduction in large and chronic RDEB wounds is undefined. To further assess reported therapeutic options, we searched PubMed for articles published from database inception to April 11, 2025, using the terms ("dystrophic epidermolysis bullosa") AND (("cell*" OR "gene*") AND ("therapy" OR "treatment")), limited to the English language. We filtered by article type "clinical trial" and identified 27 results. We then manually screened the search results for publications that assessed cell-based or gene-based therapies in the treatment of RDEB wounds. Cell-based and gene-based therapies tested in patients with RDEB included intradermal allogeneic fibroblast injections, intradermal lentiviral-based *COL7A1*-corrected autologous fibroblasts, intravenous allogeneic bone marrow-derived mesenchymal stem cells, allogeneic bone marrow transplantation, beremagene geperpavec, and prademagene zamikeracel (formerly EB-101), the focus of this study. Treatment with a single intradermal allogeneic fibroblast injection to RDEB wounds has been assessed in several early open-label trials. Despite an adequate safety profile and increased type VII collagen in a few patients, studies showed mixed results in terms of wound healing, with improved wound healing most notably reached in patients already expressing some degree of type VII collagen in the skin. A phase 1 study assessing single intralesional injection of lentiviral-based *COL7A1*-corrected autologous fibroblasts showed the restoration of type VII collagen expression in treated RDEB wounds; however, no new mature anchoring fibrils were formed. Beremagene geperpavec is a topical gene therapy consisting of wild-type *COL7A1*-containing Herpes simplex virus type 1 (HSV-1) vector for dystrophic epidermolysis bullosa. In its phase 1/2 trial, beremagene geperpavec showed safety, restoration of type VII collagen expression in treated wounds, and wound healing. Findings were further corroborated in its phase 3 trial, in which beremagene geperpavec significantly outperformed placebo in terms of complete wound healing at the 3-month and 6-month timepoints yet did not show a significant reduction in pain. Adverse events associated with beremagene geperpavec were mild, and although some patients developed anti-HSV-1 and anti-COL7 antibodies after beremagene geperpavec application, the efficacy of beremagene geperpavec was maintained at 6 months. Beyond locally administered therapeutic options, systemic treatment modalities have also been tested in patients with RDEB. Intravenously injected allogeneic mesenchymal stromal cells derived from bone marrow and umbilical cord blood were assessed in several phase 1/2 studies. Despite an acceptable safety profile and improvements in overall disease activity including outcomes such as wound healing, pain, and itch, the clinical benefits of mesenchymal stromal cells were transient and variable across studies. In patients with severe RDEB, treatment with allogeneic bone marrow transplantation led to a durable increase in type VII collagen in the skin, improved overall wound healing, and a reduction in wound dressing requirements. However, bone marrow transplantation was associated with considerable morbidity and mortality (approximately 20%). Prademagene zamikeracel is an autologous sheet of *COL7A1* gene-corrected keratinocytes that aims to address the unmet clinical need in large, chronic RDEB wounds. In a pivotal phase 1/2a open-label clinical trial, prademagene zamikeracel was shown to be safe, promoted type VII collagen expression and durable wound healing up to 8 years, and showed improved patient-reported outcomes of pain and itch.

Added value of this study

VIITAL is the first phase 3, randomised, intrapatient-controlled trial in patients with RDEB to investigate the safety and efficacy of prademagene zamikeracel for large, chronic RDEB wounds. Our results of improved wound healing and pain versus control will help bolster the evidence in favour of prademagene zamikeracel as an autologous cell-based gene therapy tailored to the long-term treatment of skin wounds in patients with RDEB. There are no approved treatments that have shown sustained wound healing and pain reduction for large, chronic RDEB wounds. These wounds are much more difficult to treat and, unlike smaller wounds, do not heal spontaneously.

Implications of all the available evidence

VIITAL provides the evidence needed to establish the safety and efficacy of prademagene zamikeracel in healing large, chronic wounds and reducing pain in patients with RDEB. These results have clinical practice-changing implications and support the use of prademagene zamikeracel as treatment for large, chronic wounds in patients with RDEB.

These wounds are difficult to treat and, unlike recurrent wounds, do not heal spontaneously and are the wounds that are most clinically meaningful to patients.[15–17]

Cell therapy with genetically modified epidermal stem cells was first shown in a single patient with *LAMB3*-deficient junctional epidermolysis bullosa.[18] We developed prademagene zamikeracel (formerly EB-101) as a one-time surgical application of *COL7A1*-corrected autologous keratinocyte sheets to heal RDEB wounds.[19] In a previous phase 1/2a open-label study and subsequent

long-term follow-up study, prademagene zamikeracel showed preliminary safety and wound healing in seven patients for up to 8 years.[19,20] We aimed to use matched chronic wound pairs to assess the effect of prademagene zamikeracel on wound healing and wound pain 24 weeks after surgical application of prademagene zamikeracel.

Methods

Study design

VIITAL was a randomised, open-label, intrapatient-controlled phase 3 trial conducted in children and adults with RDEB at two institutions (Stanford University and University of Massachusetts) in the USA and was approved by both sites' institutional review boards (Federalwide Assurance FWA00000935, Institutional Review Board Registration IRB00000348). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and applicable local regulatory requirements and laws. This trial was registered with ClinicalTrials.gov (NCT04227106); patients are being followed up for 15 years after treatment in a long-term, follow-up study (NCT05708677). The protocol and statistical analysis plan, along with amendments, are provided.

Participants

Given that RDEB is a rare disease, this trial used an intrapatient design in which wounds were randomly assigned either to treatment or control within a prespecified wound pair. Wounds within a pair were matched by wound chronicity, location, and size, if possible. Eligible patients were aged 6 years or older, had a confirmed clinical and genetic diagnosis of RDEB, and had no evidence of an immune response to type VII collagen. To reduce the likelihood of developing an immune response to the treatment, only patients who expressed the amino-terminal NC1 fragment of type VII collagen and did not have circulating antibodies to type VII collagen by indirect immunofluorescence on monkey oesophagus and western blot were enrolled, similar to previous studies.[19,21] Furthermore, patients should not have received any biological or chemical RDEB-specific product for at least 3 months before the commencement of the study. Patients could not enrol in any other trial and could not receive other experimental treatments. Patients were recruited from epidermolysis bullosa clinic centres in the USA. At least two matched eligible wound sites were required. Eligible wounds were 20 cm² or larger, present for 6 months or more, and without history or current clinical evidence of squamous cell carcinomas. A maximum of six wounds could be treated with prademagene zamikeracel per patient. This upper limit of six *COL7A1*-corrected sheets was a safety mandate by the FDA and was consistent with the manufacturing process used in the phase 1/2a trial. If a patient had fewer than six wound pairs, additional wounds were considered for prademagene zamikeracel treatment as non-randomised wounds. Written informed consent was obtained from each patient or their legal guardian.

Randomisation and masking

At the screening and baseline visits (1 day before surgical application), investigators selected wound pairs matched by similar size, chronicity, and anatomical region in each patient. Matched wounds within each pair were randomly assigned (1:1) to prademagene zamikeracel treatment or control (standard of care) by computer randomisation using an electronic data capture system (Medrio versions 40.3 to 41.5.7); each wound in the wound pair was given the same probability of receiving treatment or control. The randomisation schedule was generated by a staff statistician who was not involved with patient enrolment or the clinical trial. The randomisation assignments for all wound pairs were provided by the electronic data capture system. As visible prademagene zamikeracel sheets were sutured onto wounds, this study could not be masked for the patient or investigator.

Procedures

As previously described in the phase 1/2a trial,[19,22] primary autologous patient keratinocytes were cultured from two 8 mm punch biopsies obtained from non-wounded, non-blistered skin. Isolated keratinocytes were transduced with a retrovirus carrying the full-length human *COL7A1* gene and cultured to form 40 cm² keratinocyte sheets (prademagene zamikeracel). Prademagene zamikeracel sheets were stapled onto petrolatum gauze to allow for transportation. After approximately 25 days, patients returned for surgical application under general anaesthesia.

Wound beds were debrided and cauterised to fit the 40 cm² size of prademagene zamikeracel and to minimise potential retained epidermal stem cells. A maximum of six wounds could be treated with prademagene zamikeracel, and each sheet was sutured onto the debrided wounds with absorbable sutures.[23] Consistent with the phase 1/2a study, control wounds were not debrided to prevent potential wound expansion and associated potential complications after debridement. Wounds smaller than 40 cm² had to be expanded or debrided to fit the 40 cm² size of the prademagene zamikeracel sheets. Prademagene zamikeracel sheets could not be cut into smaller sheets following validated manufacturing processes and previous safety and efficacy results from the phase 1/2a study.

Patients were hospitalised for 7 days after surgery to ensure protection of prademagene zamikeracel sheets from pressure and friction. During hospitalisation, the prademagene zamikeracel-treated wounds were first covered with non-adhesive contact dressings, and then an outer absorbent foam dressing layer held in place with rolled gauze, as is standard of care. To optimise

prademagene zamikeracel treatment, the contact dressing layer was not changed during hospitalisation. After approximately 14 days, the gauze backing of prademagene zamikeracel fell off once the absorbable sutures dissolved. Patients and caregivers were provided with written instructions on home care of treated and control wounds. Control wounds were not surgically debrided in the operating room due to concerns of potential expansion of the open wound. Control and treated wounds used standard of care dressing protocols during the 7-day hospitalisation and for one additional month. After a month, wounds were treated according to the patient's normal home regimen. Follow-up visits occurred at weeks 2, 4, 6, 9, 12, 18, 24, and 26. Throughout the follow-up period, concomitant medications and adverse events were assessed at every visit with pain, itch, wound healing, and patient and caregiver-reported outcomes collected in accordance with the protocol.

Outcomes

The first coprimary endpoint was the proportion of wounds with at least 50% healing from baseline at week 24, as determined by an in-clinic investigator global assessment, with confirmation of sustained wound healing at a subsequent visit. The second coprimary endpoint was the mean change in pain at week 24 from baseline. Wound pain was assessed with the Wong-Baker Faces pain scale scores within 3 h after wound dressing change. Mean change in pain was added as a coprimary endpoint in accordance with FDA comments in version 6 of the protocol.

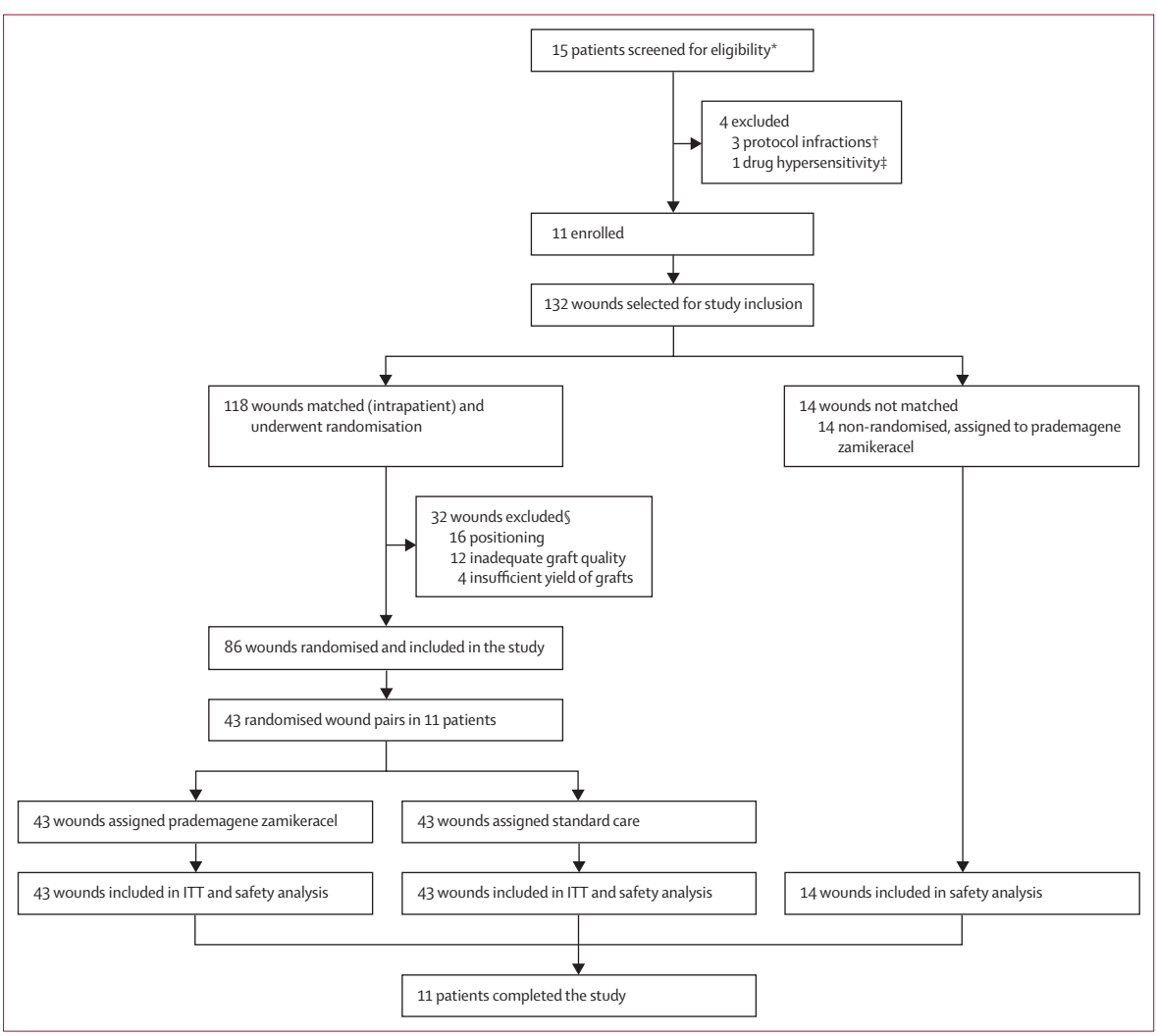

Figure 1: **Trial profile**
ITT=intention-to-treat. *Four patients were rescreened due to disruptions caused by COVID-19 or issues with the prademagene zamikeracel sheet manufacturing; all four patients subsequently were enrolled in the study and received prademagene zamikeracel treatment. †Inability to properly follow protocol as determined by the principal investigator. ‡Hypersensitivity to vancomycin. §Includes both treated and control wounds since the exclusion of one wound automatically excludes its paired control wound.

The secondary endpoint was the proportion of randomly assigned wounds with complete healing at week 12 and at week 24. Complete wound healing was strictly defined as wounds with complete re-epithelisation without visible drainage or erosions and with only the presence of minor crusting. Key exploratory endpoints included additional measures of wound healing (≥50% and ≥75% healing at week 12; ≥75% healing at week 24), pain severity scored for each study wound (at-home pain diary, Wong-Baker Faces at week 12) and for the patient (Patient-Reported Outcomes Measurement Information System [PROMIS] pain quality; PROMIS pain interference), and wound itch severity (Worst Itch Numeric Rating Scale). The appendix contains the full exploratory endpoints (pp 86–87). Caregiver Global Impression of Pain score and Patient Global Impression of Change-Blistering were scored by percentage of wounds categorised as much or very much improved from baseline.

Baseline control and treated wounds were digitally photographed with a ruler immediately following debridement of treated wounds at baseline. For each wound pair, as well as additional wounds treated with prademagene zamikeracel, a minimum of five images were captured from multiple angles. At follow-up, the principal investigator evaluated wound healing by direct visual comparison of the wound and comparing the wound to the baseline photograph. Healing was defined as the appearance of any epithelialised skin free of wounding, blistering, or erosions. The extent of healing was categorised as: (1) less than 50% of baseline; (2) 50% to less than 75% of baseline; and (3) 75% or more of baseline, with complete wound closure assessed if healing reached 75% or more of baseline.

All patients were monitored for adverse events that emerged or worsened after study participation via patient report, physical examination, vital signs, and clinical laboratory tests, including serum assays to detect systemic replication-competent retrovirus at screening and weeks 6, 12, and 24. Adverse event severity was graded by investigators according to the Medical Dictionary for Regulatory Activities version 23.0. Analyses of adverse events were based on the safety population using all evaluated wounds, both those randomly assigned and those not.

Statistical analysis

A sample size consisting of a minimum of 36 wound pairs (72 wounds) in at least ten patients was estimated based on wound healing results obtained from the phase 1/2a trial.[19] Statistical power calculations for rejecting the first coprimary endpoint assumed an 84% probability for wound healing in wounds treated with prademagene zamikeracel and 39% for control wounds. For the second coprimary endpoint, the probability of pain reduction was assumed at 84% for wounds treated with prademagene zamikeracel and 50% for control wounds. Joint statistical power for the trial was bounded by the multiplication of these two conservative powers and expected to be more than 80%. A detailed power calculation is presented in the appendix (pp 2–3).

The intention-to-treat population (coprimary and exploratory secondary endpoints) included all patients and randomised wounds. The safety analysis population included all patients and evaluated wounds, randomised and non-randomised. To reach an unbiased estimation of the difference in healing rates and pain reduction between treated and untreated wound sites for each wound pair, the difference between prademagene zamikeracel and control wound sites was calculated first for each wound. The difference was then averaged across

See Online for appendix

	Patients (n=11)
Age, years	21 (17–30)
Sex	
Male	4 (36%)
Female	7 (64%)
Race	
White	10 (91%)
Other (unknown)	1 (9%)
Ethnicity	
Hispanic or Latino	2 (18%)
Not Hispanic or Latino	8 (73%)
Not reported	1 (9%)
RDEB subtype*	
Severe	4 (36%)
Intermediate	7 (64%)
Total number of wounds	86
Number of wounds randomly assigned to prademagene zamikeracel	43/86 (50%)
Wound duration, years	5 (<1–10)
Pain severity†	4 (2–8)
Itch severity‡	4 (2–8)
Wounds by anatomical region	
Anterior trunk	18/43 (42%)
Posterior trunk	10/43 (23%)
Arms	8/43 (19%)
Legs	7/43 (16%)
Number of wounds randomly assigned to control	43/86 (50%)
Wound duration, years	5 (<1–10)
Pain severity†	4 (2–6)
Itch severity‡	4 (2–8)
Wounds by anatomical region	
Anterior trunk	4/43 (9%)
Posterior trunk	23/43 (53%)
Arms	5/43 (12%)
Legs	11/43 (26%)

Data are median (IQR), n (%), n, or n/N (%). RDEB=recessive dystrophic epidermolysis bullosa. *Classification is based on the classification proposed by Has and colleagues. †Range of Wong-Baker Faces pain scale from 0 (no pain) to 10 (worst pain) with intervals of 2. ‡Range of Worst Itch-Numeric Rating Scale from 0 (no itch) to 10 (worst itch) with intervals of 2.

Table 1: **Patient demographics and baseline wound characteristics of the intention-to-treat population**

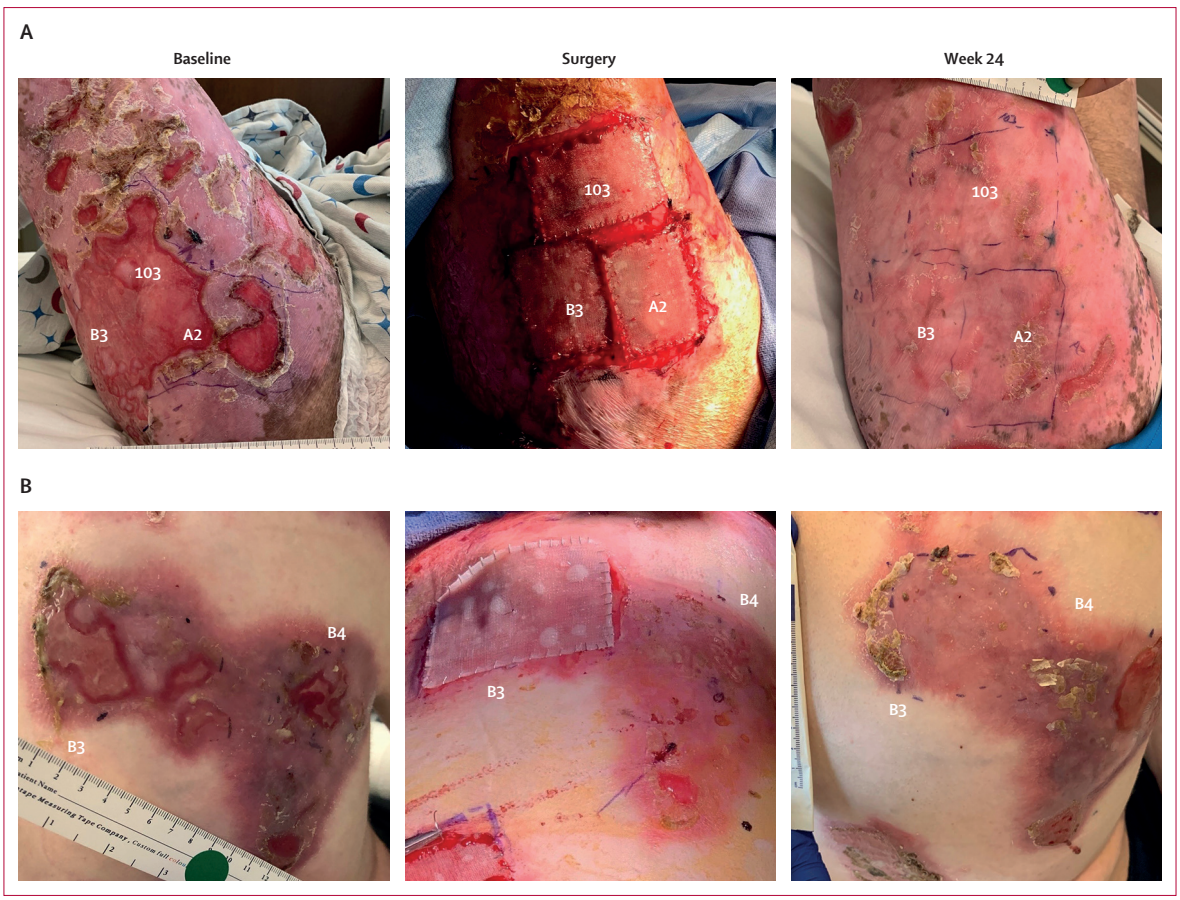

Figure 2: **Representative images of wounds randomly assigned to prademagene zamikeracel or control at baseline, surgery, and week 24**
Photographs of wounds at baseline and at designated timepoints after treatment. During surgery, randomised wounds treated with prademagene zamikeracel were debrided to fit the 40 cm² prademagene zamikeracel sheets. Small (approximately 1 mm) tattoo dots were placed at the four corners of the prademagene zamikeracel sheet and the edges of control wound areas during surgery for identification of treated sites at follow up visits. (A) Three adjacent prademagene zamikeracel sheets (designated as B3, A2, and 103) that were placed on a large, confluent wound on one patient's lateral left thigh. All three wound areas were rated as at least 75% healed at week 24. (B) A different patient in whom the paired matched wounds are located next to each other on their right medial and lateral scapula. The B3 wound was randomly assigned to prademagene zamikeracel treatment and rated as at least 75% healed at week 24. A marker was used to outline the edges of the engrafted prademagene zamikeracel sheet. The B4 wound was randomly assigned to control (standard of care treatment) and was rated as less than 50% healed at week 24 compared with the baseline wound image.

all matched pairs within a patient, and then the average rate was averaged across all patients.

The last observation carried forward method was used for imputing any missing data. A generalised estimation equation (GEE) approach was used to estimate treatment effect. To test coprimary and secondary endpoints, a permutation test based on the GEE framework was used, whereby the responses within each patient were averaged to derive a single summary measure, and then the averages were aggregated across patients to assess the overall treatment effect in the context of potential intrapatient correlation. The null hypothesis was rejected at a two-sided 5% significance level. Concerning the safety analysis for patients, the 95% CIs for the proportions of patients with at least one systemic treatment emergent adverse event was derived using the Wilson score interval method. For the wound safety analysis, the proportion of wound-related local adverse events in each group was determined with the Wilson score interval method. The risk difference between the groups and its associated 95% CIs used the Newcombe method. Formal statistical inferences on exploratory endpoints were performed post hoc. All statistical analyses were performed with SAS, version 9.4. There was no data monitoring committee.

Role of the funding source

Authors from the funder of the study (Abeona Therapeutics) collaborated with academic investigators on the study design, data review, data interpretation, and writing of the Article. Data analysis was conducted by the funder with external parties for data management, data integrity, and statistical analyses (Pharmapace and YBR Analytics).

Results

All 11 patients with RDEB, enrolled from Jan 1, 2020, to March 31, 2022, completed the trial (figure 1). 86 wounds

were matched and randomised: 43 (50%) to prademagene zamikeracel and 43 (50%) to control (standard care). 14 wounds were not matched or randomised but were assigned to prademagene zamikeracel. Four (36%) of 11 participants were male and seven (64%) of 11 participants were female. The median patient age was 21 years and their wounds (n=86) had been present for a median of 5 years (table 1). Additional baseline characteristics for each wound are presented in the appendix (p 6).

At week 24, the first coprimary endpoint of at least 50% healing from baseline was observed in 35 (81%) of 43 wounds treated with prademagene zamikeracel compared with seven (16%) of 43 control wounds (mean difference 67% [95% CI 50–89], p<0·0001; table 2). Figure 2 shows representative images of selected prademagene zamikeracel treated wounds at baseline, surgery, and at week 24. The coprimary endpoint of at least 50% healing from baseline is also shown for wounds of each participant in the appendix (p 7).

The second coprimary endpoint of change in pain severity was also met. At study visits, pain was assessed for each wound after dressing change. The mean change in pain from baseline to week 24 was –3·07 with prademagene zamikeracel and –0·90 in control wounds (mean pairwise difference –2·23 [95% CI –3·45 to –0·66], p=0·0002; table 3). Baseline and week 24 change in pain severity outcomes for treated and control wounds in each wound pair along with associated differences are shown in the appendix (p 8).

The secondary endpoint of complete wound healing from baseline was observed in six (14%) of 43 prademagene zamikeracel wounds at week 12 (mean difference 19% [95% CI 3–42], p=0·032) and seven (16%) of 43 prademagene zamikeracel wounds at week 24 (mean difference 13% [95% CI 2–26], p=0·016) compared with 0% of control wounds at both timepoints (table 2). Exploratory endpoints of wound healing at least 75% from baseline occurred in 20 (47%) of 43 prademagene zamikeracel wounds at week 12 (mean difference 39% [95% CI 20–67], p=0·0001) and 28 (65%) of 43 prademagene zamikeracel wounds at week 24 (mean difference 58% [95% CI 34–82], p<0·0001) compared with three (7%) of 43 control wounds at both timepoints (table 2).

23 (53%) of 43 control wounds and ten (23%) of 43 prademagene zamikeracel wounds were located on the posterior trunk (table 1). However, the percentage of prademagene zamikeracel wounds that had at least 50% healing at week 24 was similar for wounds on the posterior trunk (90%) and treated wounds in all other locations (90%; appendix p 9).

Pain assessed within 3 h after dressing change was reduced in prademagene zamikeracel wounds compared with control wounds at week 12 (mean pairwise difference –2·02 [95% CI –3·33 to –0·44], p=0·0006; table 3). At-home pain diaries also showed pain reduction for wounds treated with prademagene zamikeracel (appendix p 5). At week 24, there was a reduction in PROMIS Pain Quality sensory scores in prademagene zamikeracel wounds compared with control wounds (mean change –3·3 *vs* –0·5; mean pairwise difference –2·84 [95% CI –5·25 to –0·38], p=0·0093), and a trend toward reduction in PROMIS Pain Quality affective scores (mean change –1·4 *vs* –0·5; mean pairwise difference –0·94 [95% CI –2·53 to 0·51], p=0·12; appendix p 10).

The mean change in itch severity from baseline to week 24 was –2·0 for prademagene zamikeracel wounds compared with –0·5 for control wounds (mean pairwise difference –1·56 [95% CI –2·95 to –0·26; p=0·0044; appendix p 9). Patients also reported that blistering was much or very much improved in 67% of wounds randomly assigned to prademagene zamikeracel, compared with 12% of control wounds (mean

	Prademagene zamikeracel (n=43)	Control (n=43)	Mean difference in healing proportions, % (95% CI)*	p value†
Wound healing at week 24‡				
≥50% from baseline	35 (81%)	7 (16%)	67% (50–89)	<0·0001
≥75% from baseline	28 (65%)	3 (7%)	58% (34–82)	<0·0001
Complete healing	7 (16%)	0	13% (2–26)	0·016
Wound healing at week 12				
≥50% from baseline	34 (79%)	8 (19%)	62% (41–84)	<0·0001
≥75% from baseline	20 (47%)	3 (7%)	39% (20–67)	0·0001
Complete healing	6 (14%)	0	19% (3–42)	0·032

Data are n (%), unless otherwise stated. Wound healing in control wounds was measured relative to the baseline wound size (minimum of 20 cm^2) at day –1. For prademagene zamikeracel-treated wounds, wound healing was measured relative to the debrided wound size (40 cm^2) at day 0, which was the wound area after surgical debridement to fit the 40 cm^2 prademagene zamikeracel sheet. For control wounds, there was no surgical debridement of the wound bed. *Determined by first calculating the difference between healed and not healed for each wound pair; next, the wound-pair differences were averaged within each patient, resulting in patient averages; finally, these patient averages were averaged across all patients to calculate the final mean paired difference in healing proportions. †Calculated using a randomisation test; p value is the proportion of the absolute differences (two-sided) generated by permutations that equal or exceed the observed absolute difference. ‡Wounds with a healing category at week 24 were required to be confirmed at a subsequent visit.

Table 2: **Wound healing as determined by direct investigator assessment in clinic**

	Prademagene zamikeracel (n=43)	Control (n=42)†	Mean pairwise difference (95% CI)‡	p value§
Change in pain from baseline to week 24	–3·07	–0·90	–2·23 (–3·45 to –0·66)	0·0002
Change in pain from baseline to week 12	–2·60	–0·86	–2·02 (–3·33 to –0·44)	0·0006

*Pain was assessed primarily via the Wong-Baker Faces scale (range 0–10, with intervals of 2) during clinic visits; however, before protocol version 6, the numerical rating scale was used; for every post-baseline visit, the change in pain was calculated as post-baseline pain score minus the baseline pain score; no additional pain medication outside of the patients' routine pain medication were taken before the pain assessment. †One control wound had missing data at baseline for wound pain. ‡Determined by first calculating the change in pain for each wound (a negative value represented pain reduction and a positive value represented pain worsening); next, the wound-pair differences in pain reduction (treated minus control) were averaged within each patient resulting in patient averages; finally, these patient averages were averaged across all patients to calculate the final mean paired difference in pain reduction scores. §The significance of the observed difference (p value) was calculated with a randomisation test; the p value is the proportion of the absolute differences (two-sided) generated by permutations that equal or exceed the observed absolute difference.

Table 3: **Mean change in pain reduction* during or after wound dressing change**

	Patients (n=11)
Total number of adverse events	104
Patients with at least one adverse event†	11 (100%)
Mild	6 (55%)
Moderate	11 (100%)
Severe	2 (18%)
Life-threatening or debilitating	0
Fatal	0
Related to prademagene zamikeracel	4 (36%)
Leading to discontinuation of prademagene zamikeracel	0
Adverse events reported in at least 10% of patients†‡	
Wound infection	8 (73%)
Procedural pain	6 (55%)
Constipation	3 (27%)
Pruritus	3 (27%)
COVID-19 infection	2 (18%)
Upper respiratory tract infection	2 (18%)
Back pain	2 (18%)

Data are n (%). *Data are for adverse events that emerged or worsened after the one-time application of prademagene zamikeracel. †At each classification level, a patient was counted once if one or more events occurred. ‡Adverse events were coded with Medical Dictionary for Regulatory Activities version 23.0.

Table 4: **Summary of adverse events in the safety population***

difference 59% [95% CI 42 to 83], p<0·0001; appendix p 10). Caregiver Global Impression of Pain scores at week 24 showed that prademagene zamikeracel wounds were much or very much improved compared with baseline in five (45%) of 11 patients. There were no reports of much or very much improved pain in control wounds for any patient (p=0·063; appendix p 11).

Although all patients had at least one adverse event, the majority of adverse events were mild or moderate in severity (table 4; appendix p 13). Only five adverse events occurring in two patients were serious: one patient had three instances of severe wound infection and had a non-healing ulcer necessitating a left toe amputation, and another patient had a squamous cell carcinoma on their hand, an anatomical location that had not been exposed to prademagene zamikeracel. None of the serious adverse events were considered related to prademagene zamikeracel treatment by the investigators. Four patients had adverse events related to prademagene zamikeracel treatment: procedural pain (two patients), muscle spasms (one patient), and pruritus (one patient). None of the adverse events related to prademagene zamikeracel were severe, and all resolved without sequelae. No deaths were reported, and no patients discontinued the trial. No systemic replication-competent retrovirus was detected in patient serum at any follow-up visit. There was no evidence of systemic immunological response or squamous cell carcinomas at any study wound randomly assigned to prademagene zamikeracel.

Wound-related adverse events were reported in 22 (39%) of 57 prademagene zamikeracel wounds (seven patients, randomised and non-randomised wounds) and seven (16%) of 43 control wounds (four patients; appendix p 14). None were severe or led to new or long-term hospitalisation. 20 instances of wound infection were reported in 12 (21%) of 57 prademagene zamikeracel wounds (five patients), compared with four instances of wound infection in four (9%) of 43 control wounds (three patients); all were mild or moderate. Procedural pain was noted in ten (18%) of 57 prademagene zamikeracel wounds (two patients) and three (7%) of 43 control wounds (one patient). Adverse events unrelated to study wounds are summarised in the appendix (p 15).

Discussion

In this phase 3, randomised, intrapatient-controlled trial, RDEB wounds treated with prademagene zamikeracel sheets showed better healing compared with control wounds. Wounds treated with prademagene zamikeracel had less pain compared with control wounds. Both coprimary endpoints of at least 50% wound healing and pain reduction at week 24 were met.

Concerning our coprimary endpoint of mean change in pain, a two-point reduction in pain was established as the cutoff for clinical relevance under FDA guidance and has been corroborated by several studies.[24,25] In one study of paediatric patients presenting with acute pain of any cause, a two-point reduction corresponded with the perception of much less pain.[24] The greater than two-point reduction in pain with prademagene zamikeracel treatment suggests that prademagene zamikeracel might be clinically effective in reducing wound pain.

Wounds on the back tend to be larger than wounds in other locations,[17] likely due to increased friction from sitting and sleeping. Large wounds pose a treatment challenge, as they are more likely to be chronic and are associated with increased pain, pruritus, and infection frequency.[17] In VIITAL, posterior trunk-prademagene zamikeracel-treated wounds had similar levels of at least 50% healing at week 24 as prademagene zamikeracel-treated wounds in all other locations.

In a 2022, phase 3 trial (GEM-3) of the topical, herpes simplex virus-based gene therapy beremagene geperpavec (Vyjuvek), 67% of treated wounds and 23% control wounds were completely healed at 24 weeks.[13] Cross-trial comparisons in general are challenging, particularly when there are differences in wound selection criteria (eg, size and chronicity), methods, and blinding. The percentage of chronic wounds and the duration of enrolled wounds in GEM3 is unclear. However, 23 (74%) of 31 wounds were less than 20 cm².[13] By contrast, VIITAL treated large chronic wounds (>20 cm²), which are less likely to heal spontaneously than smaller wounds.[26] Prademagene zamikeracel

treatment also showed improvement in patient-reported itch and blistering similar to the results in the multiyear follow-up from the phase 1/2a trial.[19]

Wound healing and pain, the focus of this study, are salient and interdependent outcomes. Chronic wounds are associated with a large wound size and tend to be more painful and pruritic than recurrent wounds.[2] Chronic wounds in patients with RDEB are characterised by persistent inflammation driven by prolonged neutrophil infiltration, impaired macrophage function, imbalances in cytokine profiles, and a propensity for persistent bacterial infections;[3] these factors contribute to a delay in wound healing and intensify wound pain and itch. A vicious cycle ensues with increases in chronic wound size exacerbating pain and itch, which in turn trigger scratching and a further impairment in wound healing. Individuals with RDEB and their caregivers report that reducing pain and accelerating wound healing and closure are the most important factors for any treatment.[7] In our study, pain of wounds treated with prademagene zamikeracel was also reduced in patient home pain diaries and PROMIS Pain Quality sensory assessment.

Treatment with prademagene zamikeracel was safe and well tolerated, with few, non-serious treatment-related adverse events, consistent with previous clinical trials.[19,20] There was no evidence of systemic retrovirus as all replication-competent retrovirus tests were negative. Most treatment-related adverse events, most commonly surgical pain, arose due to the surgical application procedure rather than from the prademagene zamikeracel sheets themselves. Muscle spasm was another reported adverse event that most likely emerged secondary to patients' efforts to minimise movement and protect prademagene zamikeracel sheets from friction or pressure during the 7-day post-surgical hospitalisation.

Wound infections are a well known and frequent occurrence in patients with RDEB.[3] Although there were more infections in wounds randomly assigned to prademagene zamikeracel than control, all infections were mild or moderate and deemed unrelated to prademagene zamikeracel. To promote keratinocyte cell engraftment during the 7-day hospital stay, prademagene zamikeracel wound sites were left undisturbed, without changing the contact layer dressings. Control sites, however, could have received more frequent dressing changes, which could explain the difference in infection rates.

One patient developed cutaneous squamous cell carcinomas during the trial at a wound site that was not treated with prademagene zamikeracel. The squamous cell carcinoma biopsy sample did not contain proviral genome sequences, and the patient was negative for systemic replication-competent retrovirus on serum testing across all assessed timepoints. Although insertional mutagenesis has occurred with other gene therapies,[27] insertional mutagenesis has not been observed with prademagene zamikeracel treatment to date.

There are several limitations of the VIITAL clinical trial. This study enrolled a small population of 11 participants with RDEB. Although the sample size was adequate to inform results, the rarity of the disease restricts the number of patients enrolled. Participants and investigators were not blinded as treated wounds had visible keratinocyte sheets sutured to the wound bed. The absence of blinding could introduce detection and performance biases especially with self-reported symptoms, such as pain and itch. We recognise that not blinding assessments can potentially distort symptom reporting and partly result in a placebo effect despite the use of standardised evaluation procedures. An additional limitation is the randomisation process. We matched wound pairs by size, chronicity, and anatomical region, if possible, and randomised 1:1 accordingly to attempt to balance known confounding factors; however, this process is still potentially subject to selection bias and cannot completely eliminate the variability between target wound pairs. Another limitation is that wound healing images were not assessed by an independent, blinded review panel. Wound healing from baseline was scored by an in-person, clinical evaluation for each wound at weeks 12 and 24. Wound healing evaluation with photographs was not considered an acceptable method by the FDA. Control wounds were not surgically debrided unlike wounds randomly assigned to treatment, which was consistent with the phase 1/2a trial in which control wounds were not debrided to reduce the risk of wound expansion and pain. However, this difference in treated versus control wounds should bias the results towards the null hypothesis as debridement of control wounds would probably lead to wound expansion and more pain.

Another limitation was that more control wounds were located on the back, which was due to the investigators' decision to place the patient either in the supine or lateral position to reduce anaesthesia risk and to reduce skin damage from rotating the patient in the operating room. However, the effect difference in wound healing by prademagene zamikeracel versus control was maintained in wound pairs located on the back. Additionally, the study included only individuals who express the NC1 portion of type VII collagen to reduce the possibility of immunological reactions. Despite the expression of the NC1 domain in more than 60% of patients with RDEB,[9] these results might not be generalisable to all RDEB patients.[21,28] We are currently conducting a phase 3b study of prademagene zamikeracel whereby the requirement for NC1 expression has been removed as an eligibility criterion (NCT05725018). We did not measure levels of type VII collagen staining in skin biopsies from wound sites at follow-up visits as molecular correction in serial skin biopsies was previously shown in wounds treated with prademagene zamikeracel from the phase 1/2a trial

(8 [66%] of 12 biopsies at the 6-month timepoint).[22] Furthermore, additional skin biopsies from grafted sites can compromise wound healing. Moreover, antibodies titres to type VII collagen were not routinely obtained during follow-up and were only measured if a participant had a possible immune response with none of the study participants requiring further antibody testing.

With regards to the practical aspects of the treatment, the prademagene zamikeracel manufacturing process had a predictable turnaround time of approximately 24 days with occasional variability in the yield of the sheets, as expected for an autologous product. Wound pairs initially randomised were excluded due to constraints in positioning and a subsequent inability to graft prademagene zamikeracel sheets for a patient who was anaesthetised (eight wound pairs). Concerning the grafting procedure, the depth of debridement to the dermis and homogeneity of debridement was reached through expertise of the plastic surgeons without use of lasers. Prademagene zamikeracel administration requires centres of excellence with a multidisciplinary team comprising of an epidermolysis bullosa physician, anaesthesiologist, and surgeon to support prademagene zamikeracel application and after care. Finally, the durability and long-term healing in this phase 3 study beyond 6 months was not assessed per protocol. However, evidence of durability after 2 years has been shown in the phase 1/2a trial in which 27 (71%) of 38 treated wounds had 50% or greater healing compared with one (17%) of six control wounds (p=0·019).[20] Participants from this phase 3 trial have been enrolled in a separate long-term follow-up study (NCT05708677) that will provide further data as participants will be monitored for 15 years per FDA guidelines.

These results, along with evidence from the phase 1/2a trial showing wound healing and reduction of pain and itch after prademagene zamikeracel treatment for up to 8 years,[20] as well as the absence of serious treatment-related adverse events, show the favourable risk–benefit profile of prademagene zamikeracel for treatment of large, chronic wounds in patients with RDEB.

Contributors

Study conception and design: JYT, MPM, KW, and IDG. Data collection: JYT, MPM, KW, ASC, IB, NH, JN, ESG, HPL, LKF, and RKK. Analysis and interpretation of results: JYT, MPM, KW, DM, AT, ASC, ESG, EE, JKM, IDG, and YL. Draft manuscript preparation: JYT, AT, ASC, JN, ESG, EE, AJM, and IDG. JYT, EE, AJM, AT, and IDG directly accessed and verified the underlying data reported in the manuscript. All authors had access to the study data, reviewed the results, approved the final version of the manuscript, and accept responsibility for submission for publication.

Declaration of interests

JYT is listed on the patent for prademagene zamikeracel, which is licensed to Abeona by Stanford University but does not receive royalties, and has also consulted on epidermolysis bullosa-related therapeutics for BridgeBio and Fibroderm. MPM is also listed on the patent for prademagene zamikeracel but does not receive royalties; and has received grant funding from Nova Anchora, Krystal Biotech, Castle Creek, and Abeona, and receives contributions to their salary from the Office of Research and Development, Palo Alto Veterans Affairs Medical Center. KW has received grants from both Phoenicis Therapeutics and EB Research Partnership. ASC and HPL have consulted for Abeona. YL received a research grant from Abeona through Stanford University. ESG was a sub-investigator on this trial and has consulted for Abeona; was also a sub-investigator on clinical trials for Castle Creek, TWI Bio, Rheacell, Krystal Biotech, and Phoenicis; was on advisory boards for Chiesi USA, Krystal Biotech, and Abeona; and has received honoraria from Chiesi USA, and Krystal Biotech. AT and AJM are current employees of Abeona. AT is also the owner and cofounder of YBR Analytics, which received payment from Abeona for contributions to this study. DM and IDG are former employees of Abeona. All other authors declare no competing interests.

Data sharing

The datasets generated and analysed for this study are not publicly available. Abeona Therapeutics will assess requests for data from qualified external investigators for scientific merit based on potential impact on the field or patient community, rigour of planned methods, and originality of the planned research or analysis. Patient-level data will be de-identified, to respect patient privacy and conform to applicable laws and regulations. Requests for access to the data from this study can be submitted via email to medinfo@abeonatherapeutics.com. All approved requests will require an agreement with Abeona Therapeutics before release of data.

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